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(54) Title: MULTICYCLIC COMPOUNDS FOR USE AS MELANIN CONCENTRATING HORMONE ANTAGONISTS IN THE TREATMENT OF OBESITY AND DIABETES

(57) Abstract: The present invention relates to a melanin concentrating hormone antagonist compound of formula I: (I);or a pharmaceutically acceptable salt, solvate, enantiomer or prodrug thereof useful in the treatment, prevention or amelioration of symptoms associated with obesity and related diseases.

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MULTICYCLIC COMPOUNDS FOR USE AS MELANIN CONCENTRATING HORMONE ANTAGONISTS IN THE TREATMENT OF OBESITY AND DIABETES

Field of Invention

The present invention is in the field of medicine, particularly in the treatment of obesity and diseases caused by or exacerbated by obesity. More specifically, the present invention relates to antagonists of melanin concentrating hormone useful in the prevention and treatment of obesity and related diseases.

Background of the Invention

The affluence of the 90's along with the exponential increase in food production particularly in Western and Asian economies has resulted in feeding patterns that lead to obesity. Obesity is defined as being excessively overweight. Excessive weight is generally characterized by excessive body fat, because unused energy is stored in the adipose tissues as fat.

Obesity has associated with it, economic and social costs. Obese people, an increasing proportion of developed and developing societies, are regarded as having out of control feeding habits often associated with low self-esteem. Moreover, obese persons are more likely to have medical problems associated with or exacerbated by the excess body weight. Examples of medical conditions caused, exacerbated or triggered by excessive weight include bone fractures, pains in the knee joints, arthritis, increased risk of hypertension, artherosclerosis, stroke, diabetes, etc.

Background of the invention

Melanin concentrating hormone (MCH) is a 19 amino acid neuropeptide produced in the lateral hypothalamic area and zona incerta, although MCH-expressing neurons project to numerous regions of the brain. MCH is processed from a larger pre-prohormone that also includes a second peptide, NEI, and possibly a third, NGE (Nahon, Crit Rev in Neurobiology, 8:221-262, 1994). MCH mediates its effects through at least two G protein-coupled receptors, MCHR1 and MCHR2 (Saito et al. Nature 400: 265-269, 1999; Hill et al., J Biol Chem 276: 20125-20129, 2001). Both receptors are expressed in regions of the brain consistent with MCH neuronal projection and known MCH physiologic

function (Hervieu et al., Eur J Neuroscience 12: 1194-1216, 2000; Hill et al., J Biol Chem 276: 20125-20129, 2001; Sailer et al., Proc Nat Acad Sci 98: 7564-7569, 2001).

Extensive evidence exists to support the orexigenic activity of MCH. MCH mRNA is elevated in rodent models of obesity and in the fasted state (Qu et al., Nature 380: 243-247, 1996). Intracerebroventricularly administered MCH increases feeding and blocks the anorexic effect of α-melanocyte stimulating hormone (Ludwig et al., Am J Physiol 274: E627-E633, 1998). MCH knock-out mice ($MCH^{-/-}$ mice) are lean, hypophagic and hypometabolic (Shimada et al., Nature 396: 670-674, 1998), while MCH over-expressing transgenic mice are obese and insulin resistant (Ludwig et al., J Clin Invest 107: 379-386, 2001). $MCHR1^{-/-}$ mice have recently been reported to be lean and hypermetabolic, indicating that the R1 isoform mediates at least some of the metabolic effects of MCH (Marsh et al., Proc Nat Acad Sci 99: 3240-3245, 2002; Chen et al., Endocrinology, 2002, in press).

In addition to its effects on feeding, MCH has been implicated in regulation of the hypothalamic-pituitary-adrenal axis through modulation of CRF and ACTH release (Bluet-Pajot et al., J Neuroendocrinol 7: 297-303, 1995). MCH may also play a role in the modulation of reproductive function (Murray et al., J Neuroendocrinol 12: 217-223, 2000) and memory (Monzon et al., Peptides 20: 1517-1519, 1999).

The current preferred treatment for obesity as well as Type II non-insulin dependent diabetes is diet and exercise with a view toward weight reduction and improved insulin sensitivity for diabetics. Patient compliance, however, is usually poor. The problem is compounded by the fact that there are currently only two medications approved for the treatment of obesity (sibutramine, or Meridia™ and orlistat, or Xenical™.

PCT application number WO 01/21577 (JP00/06375) filed September 19, 2000, discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/21577 application claims a compound of formula A

$$Ar^1 — X — Ar — Y — N\begin{matrix} R_2 \\ R_1 \end{matrix}$$

(A)

wherein:

Ar^1 is a cyclic group that may have substituents;

X is a spacer having a main chain of 1 to 6 atoms;

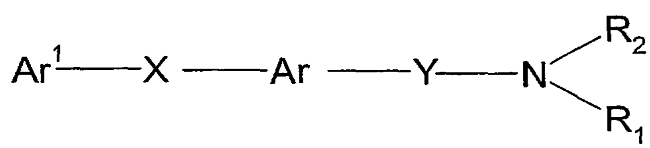
Y is a bond or a spacer having a main chain of 1 to 6 atoms;

Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents;

R^1 and R^2 together with the adjacent nitrogen atom may form a nitrogen-containing hetereo ring which may have Substituents; R^2 may form a spiro ring together with Ar; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or salts thereof.

PCT application number WO 01/82925, filed April 26, 2001, also discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/82925 application claims a compound of formula B



(B)

wherein:

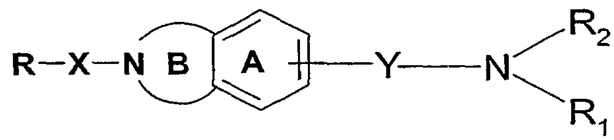
Ar^1 is an optionally substituted cyclic group;

X and Y are independently a spacer having a C_{1-6} main chain;

Ar is an optionally substituted fused polycyclic aromatic ring;

R^1 and R^2 are independently hydrogen atom or an optionally substituted hydrocarbon group; or alternatively R^1 and R^2 together with the nitrogen atom adjacent thereto may form a nitrogenous heterocycle, or R^2 together with the nitrogen atom adjacent thereto and Y may form an optionally substituted nitrogenous heterocycle, or R^2 together with the nitrogen atom adjacent thereto, Y, and Ar may form a fused ring.

PCT application number WO 01/87834, filed May 15, 2001, also discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the WO 01/87834 application claims a compound of formula C.

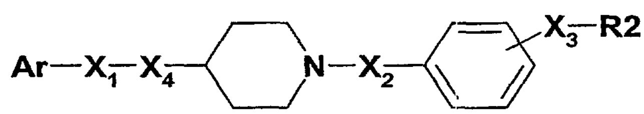


(C)

Wherein;

R represents hydrogen, halogen, or an optionally substituted cyclic group; X represents a bond or a spacer in which the main chain has one to ten atoms; Y represents a spacer in which the main chain has one to six atoms; ring A represents a benzene ring which may have other substituents; ring B represents a five- to nine-membered nitrogenous nonaromatic heterocycle which may have other substituents; and R^1 and R^2 are the same or different and each represents hydrogen, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group, or R^1 and R^2 may form an optionally substituted nitrogenous heterocycle in cooperation with the adjacent nitrogen atom and R^2 may form an optionally substituted nitrogenous heterocycle in cooperation with the adjacent nitrogen atom and Y.

Japanese patent application number JP2001-226269A also discloses compounds reportedly useful as antagonists of the MCH receptor. In particular the JP2001-226269A application claims a compound of formula D.



(D)

Wherein:

Ar is a substituted group-contg. arom. ring, X_1 is a substituted group-contg. divalent main chain of 1-5 atoms, X_2, X_3 and X_4 are linking arms, and R2 is a basic substituting group, and its salts.

Current treatments targeted at obesity have side effects. Examples of such treatments include phen-phen, and various over–the-counter appetite suppressants. These agents have not been proven effective for all patients and for sustainable periods of time. Similarly, the approved treatments, sibutramine (Meridia™) and orlistat (Xenical™) have been associated with side effects which may compromise compliance and may preclude long term use for sustained weight loss for certain patient populations.

Therefore, there is a need for new and/or improved therapeutically effective agents useful as anatagonist of melanocortin releasing hormone to better control the dietary habits, minimize the preponderance of obesity and treat, prevent and/or ameliorate the effects of obesity including for example diabetes.

Summary of Invention

The present invention relates to a compound of formula I:

$$\mathbf{Ar^1 - L^1 - Ar^2 - Ar^3 - L^2 - Q}$$

(I)

or a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer or mixture of diastereomers or prodrug thereof wherein:

Ar^1 is a cyclic group optionally substituted with one to five groups selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C_1-C_8 alkylcycloalkyl, cyano, $-(CH_2)_nNR^6R^6$, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, halo, $(CH_2)_nCOR^6$, $(CH_2)_n NR^5SO_2R^6$, $-(CH_2)_nC(O)NR^6R^6$, heterocyclic, and C_1-C_8 alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic susbstitutents are each optionally substituted with one to three groups selected from hydroxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkoxy, C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, nitro, cyano, amino, carboxamido,phenyl , aryl, alkylheterocyclic, heterocyclic, and oxo;

L^1 is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X_2-$(CR^3R^4)_m$-X_3 where X_2 is attached to Ar^1 and X_3 is attached to Ar^2 wherein R^3 and R^4 are independently selected from a bond, hydrogen, C_1-C_8 alkyl, C_2-C_8 alkylene, C_2-C_8 alkynyl, phenyl, aryl, C_1-C_8 alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substituents independently selected from oxo, nitro, cyano, C_1-C_8 alkyl, aryl, halo, hydroxy, C_1-C_8 alkoxy, C_1-C_8 halaoalkyl, $(CH_2)_nC(O)R^6$, and $(CH_2)_nCONR^6R^6$;

X_2 is independently oxygen, -CH, $-CONH(CR^3R^4)_m$, $-NHCO(CR^3R^4)_m$, $-(CR^3R^4)_m$, $-CHR^6$, $-NR^5$, S, SO, SO_2, $-O(CR^3R^4)_m$, or $-S(CR^3R^4)_m$;

X_3 is independently oxygen, -C, -CH, -CHR^6, - $(CR^3R^4)_m$, -CONH$(CR^3R^4)_m$, -NHCO$(CR^3R^4)_m$, -NR^5, -NR$^5(CR^3R^4)_m$, S, SO$(CR^3R^4)_m$, $SO_2(CR^3R^4)_m$, S$(CR^3R^4)_m$, SO, or SO_2; -O$(CR^3R^4)_m$, or –S$(CR^3R^4)_m$;

Ar^2 is a 5-member monocyclic heterocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substitutents selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkylaryl, phenyl, aryl, C_3-C_8 cycloalkyl, C_1-C_8 alkylcycloalkyl, cyano, C_1-C_8 haloalkyl, halo, $(CH_2)_nC(O)R^6$, $(CH_2)_nC(O)OR^6$, $(CH_2)_nNR^5SO_2R^6$, $(CH_2)_nC(O)NR^6R^6$, and C_1-C_8 alkylheterocyclic;

Ar^3 is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally substituted with one to three substituents independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo, -NHR^5, C_1-C_8 haloalkyl, C_3-C_8 cycloalkyl, hydroxy, alkoxy, $(CH_2)_nC(O)R^6$, $(CH_2)_nC(O)OR^6$, $(CH_2)_nNR^5SO_2R^6$, $(CH_2)_nC(O)NR^6R^6$, phenyl, C_1-C_8 alkylaryl, and aryl;

L^2 is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:

X_4-$(CR^3R^4)_m$-X_5;

wherein X_4 is attached to Ar^3 and is selected from the group consisting of C, –CH, CHR^6, -CO, O, -NR^5, -NC(O)-, -NC(S), -C(O)NR^5-, -NR$^{6'}$C(O)NR^6, -NR$^{6'}$C(S)NR^6, -SO$_2$NR^7, -NRSO$_2$R^7, and -NR$^{6'}$C(NR^5)NR^6;

X_5 is selected from the group consisting of –CH$_2$, -CH, -O(CR^3R^4)m, NR$^3(CR^3R^4)_m$, SO, SO$_2$, S, and SCH$_2$; wherein the group X_4-$(CR^3R^4)_m$-X_5 imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by -NR^{1}R^2; wherein

R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkane, C_1-C_8 alkylaryl, -C(O)C_1-C_8 alkyl, -C(O)OC_1-C_8 alkyl, C_1-C_8 alkylcycloalkane, $(CH_2)_nC(O)OR^5$, $(CH_2)_nC(O)R^5$, $(CH_2)_nC(O)NR^6R^6$, and $(CH_2)_nNSO_2R^5$; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, phenyl, and alkylaryl; and wherein R^1 and R^2 may combine together, and with the nitrogen atom to which they are attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen

containing heterocycle which may have 1, or 2 substituents independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkane, C_1-C_8 alkylaryl, -C(O)C_1-C_8 alkyl, -C(O)OC_1-C_8 alkyl, C_1-C_8 alkylcycloalkane,oxo, halo amino, and $(CH_2)_nC(O)NR^6R^6$; provided that L^2-Q is not $CONH_2$; wherein R^1 and R^2 may combine with the nitrogen atom to which they are attached to form and imine; and provided that Q is not a subsituent on an amide;

R^5 is hydrogen, CN, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_5-C_8 alkylaryl, $(CH_2)_nNSO_2C_1$-C_8 alkyl, $(CH_2)_nNSO_2$phenyl, $(CH_2)_nNSO_2$aryl, -C(O)C_1-C_8 alkyl, or -C(O)OC_1-C_8 alkyl; and

R^6 and $R^{6'}$ are each independently hydrogen, C_1-C_8 alkyl, phenyl, aryl, C_1-C_8alkylaryl, or C_3-C_8cycloalkyl;

R^7 is hydrogen, C_1-C_8 alkyl, phenyl, aryl, C_1-C_8alkylaryl, or C_3-C_8cycloalkyl, and wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

The present invention also relates to pharmaceutical formulations containing, a compound of formula I.

In another embodiment, the pharmaceutical formulation of the present invention may be adapted for use in treating obesity and related diseases.

The present invention also relates to methods for treating obesity in a patient in need thereof, wherein such treatment comprises administering to said patient a therapeutically effective amount of a compound of formula I in association with a pharmaceutically acceptable carrier, diluent or excipient.

The present invention also relates to a method for antagonizing the binding of MCH to MCH receptors for the treatment of diseases caused, or exercabated by melanin concentrating hormone.

The present invention provides the use of a compound of formula I as an appetite suppressant and/or as a weight loss agent.

The present invention is related to the use of a compound of formula I for the manufacture of a medicament for treating obesity and related diseases.

Detailed Description

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

The term "main chain" as used herein describes the number of atoms in the shortest distance between two ends of a variable or radical and includes the distance in number of atoms when traversing a straight chain, branched chain or atoms in a mono or bicyclic ring from one end of the variable or radical to the other.

The term "C_1-C_8 alkyl" represents a straight, branched hydrocarbon moiety having from one to eight carbon atoms, including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, hexyl, and the like.

The term "C_3-C_8 cycloalkyl" as used herein refers to a cyclic hydrocarbon radical or group having from 3 to 8 carbon atoms and having no double bonds. Examples of C_3-C_8 cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

The term "C_3-C_8 cycloalkenyl" as used herein referes to a cyclic hydrocarbon radical or group having from 3 to 8 carbon atoms and having from 1 to 3 double bonds. Specific examples of C_{3-8} cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, tetrahydrothiophene, tetrahydrofuran,

The term "halo" means halogens including iodo, chloro, bromo and fluoro.

The term "C_1-C_4 haloalkyl" refers to a C_1-C_4 alkyl group substituted with one, two or three halogen atoms as possible and appropriate. Examples of C_1-C_4 haloalkyl include but are not limited to trifluoromethyl, chloroethyl, and 2-chloropropyl. Similarly, a "C_1-C_8 haloalkyl" group is a C_1-C_8 alkyl moiety substituted with up to six halo atoms, preferably one to three halo atoms.

A "C_1-C_8 alkoxy" group is a C_1-C_8 alkyl moiety connected through an oxy linkage. The term includes "optionally halogenated C_{1-8} alkoxy" groups including for example, C_{1-8} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.), which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples of alkoxy groups include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy.

The term "cyclic" as used herein refers to substituted or unsubstituted aromatic and non-aromatic ring structures containing hydrocarbon groups, and substituted or unsubstituted aromatic and non-aromatic heterocyclic groups. Cyclic groups may also be monocyclic, bicyclic or polycyclic unless otherwise specified. Examples of aromatic groups include, for example, benzene, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrimidine, pyrazine, pyrimidine, pyridazine, napthyl, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4,-thiadiazole, 1,3,4-thiadiazole, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, tetrahydropyridine, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, benzofuran, benzimidazole, benzoxazole, benzothiophene, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiazine, phenoxathlin, phenoxazine, naphthylidene, quinazoline, carbazole, b-carboline, acridine, phenazine, phthalimide, and thioxanthene each of which may be optionally substituted.

The term alkylcycloalkyl" as used herein refers to an alkylgroup on which a cycloalkyl group is substituted. Exemplary of alkylcycloalkyl groups are methylcyclopropyl, methylcyclohexyl, methylcycloheptyl, ethylcyclopropyl, etc. The alkylcycloalkyl group may optionally be sustituted independently with one to five groups selected from C_1-C_8 alkyl, phenyl, aryl, halo, amino, alkysulfonyl, alkylsulfonamide, haloalkyl, carboxyalkyl, carboxamide, alkoxy, and perfluoroalkoxy.

The term "optionally substituted" as used herein and unless otherwise specified, means an optional substitution of one to five, preferably one to two groups independently selected from halo, hydroxy, oxo, cyano, nitro, phenyl, benzyl, triazolyl, tetrazolyl, 4,5-dihydrothiazolyl, halo, C_1-C_6 alkyl, C_1-C_4 haloalkyl, C_1-C_6 or a pharmaceutically acceptable salt, solvate, enantiomer, mixture of enatiomers or prodrug thereof wherein

Ar^1 is a cyclic group optionally substituted with one to five groups selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C_1-C_8 alkylcycloalkyl, cyano, $-(CH_2)_nNR^6R^6$, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, halo, $(CH_2)_nCOR^6$, $(CH_2)_n NR^5SO_2R^6$, $-(CH_2)_nC(O)NR^6R^6$,

heterocyclic, and C_1-C_8 alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic susbstitutents are each optionally substituted with one to three groups selected from hydroxy, C_1-C_8 alkoxyalkyl, C_1-C_8 haloalkoxy, C_1-C_8 alkyl, halo, C_1-C_8 haloalkyl, nitro, cyano, amino, carboxamido,phenyl , aryl, alkylheterocyclic, heterocyclic, and oxo;

L^1 is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X_2-$(CR^3R^4)_m$-X_3 where X_2 is attached to Ar^1 and X_3 is attached to Ar^2 wherein R^3 and R^4 are independently selected from a bond, hydrogen, C_1-C_8 alkyl, C_2-C_8 alkylene, C_2-C_8 alkynyl, phenyl, aryl, C_1-C_8 alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substitutents independently selected from oxo, nitro, cyano, C_1-C_8 alkyl, aryl, halo, hydroxy, C_1-C_8 alkoxy, C_1-C_8 halaoalkyl, $(CH_2)_nC(O)R^6$, and $(CH_2)_nCONR^6R^6$;

X_2 is independently oxygen, -CH, -CONH$(CR^3R^4)_m$, -NHCO$(CR^3R^4)_m$, - $(CR^3R^4)_m$, -CHR^6, -NR^5, S, SO, SO_2, -O$(CR^3R^4)_m$, or –S$(CR^3R^4)_m$;

X_3 is independently oxygen, -C, -CH, -CHR^6, - $(CR^3R^4)_m$, -NR^5, S, SO, or SO_2;

Ar^2 is a 5-member monocyclic heterocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substitutents selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkylaryl, phenyl, aryl, C_3-C_8 cycloalkyl, C_1-C_8 alkylcycloalkyl, cyano, C_1-C_8 haloalkyl, halo, $(CH_2)_nC(O)R^6$, $(CH_2)_nC(O)OR^6$, $(CH_2)_nNR^5SO_2R^6$, $(CH_2)_nC(O)NR^6R^6$, and C_1-C_8 alkylheterocyclic;

Ar^3 is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally substituted with one to three substituents independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo, -NHR^5, C_1-C_8 haloalkyl, C_3-C_8 cycloalkyl, hydroxy, alkoxy, $(CH_2)_nC(O)R^6$, $(CH_2)_nC(O)OR^6$, $(CH_2)_nNR^5SO_2R^6$, $(CH_2)_nC(O)NR^6R^6$, phenyl, C_1-C_8 alkylaryl, and aryl;

L^2 is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:

X_4-$(CR^3R^4)_m$-X_5;

wherein X_4 is selected from the group consisting of C, –CH, CHR^6, -CO, O, $-NR^5$, -NC(O)-, -NC(S), $-C(O)NR^5$-, $-NR^{6'}C(O)NR^6$, $-NR^{6'}C(S)NR^6$, $-SO_2NR^7$, $-NRSO_2R^7$, and $-NR^{6'}C(NR^5)NR^6$;

X_5 is selected from the group consisting of $-CH_2$, -CH, $-O(CR^3R^4)m$, $NR^3(CR^3R^4)_m$, SO, SO_2, S, and SCH_2; wherein the group $X_4-(CR^3R^4)_m-X_5$ imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by $-NR^1R^2$; wherein

R^1 and R^2 are independently hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkane, C_1-C_8 alkylaryl, -C(O)C_1-C_8 alkyl, -C(O)OC_1-C_8 alkyl, C_1-C_8 alkylcycloalkane, $(CH_2)_nC(O)OR^5$, $(CH_2)_nC(O)R^5$, $(CH_2)_nC(O)NR^6R^6$, and $(CH_2)_nNSO_2R^5$; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, phenyl, and alkylaryl; and wherein R^1 and R^2 may combine together, and with the nitrogen atom to which they are attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen containing heterocycle which may have 1, or 2 substituents independently selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkane, C_1-C_8 alkylaryl, -C(O)C_1-C_8 alkyl, -C(O)OC_1-C_8 alkyl, C_1-C_8 alkylcycloalkane,oxo, halo amino, and $(CH_2)_nC(O)NR^6R^6$; provided that L^2-Q is not $CONH_2$; wherein R^1 and R^2 may combine with the nitrogen atom to which they are attached to form and imine; and provided that Q is not a subsituent on an amide;

R^5 is hydrogen, CN, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_5-C_8 alkylaryl, $(CH_2)_nNSO_2C_1$-C_8 alkyl, $(CH_2)_nNSO_2$phenyl, $(CH_2)_nNSO_2$aryl, -C(O)C_1-C_8 alkyl, or -C(O)OC_1-C_8 alkyl; and

R^6 and $R^{6'}$ are independently hydrogen, C_1-C_8 alkyl, phenyl, aryl, C_1-C_8alkylaryl, or C_3-C_8cycloalkyl; wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

where R^7 is independently at each occurrence H, C_1-C_6 alkyl, phenyl or benzyl and R^8 is independently at each occurrence C_1-C_6 alkyl, phenyl or benzyl.

The term "heterocycle or heterocyclic" represents a stable, saturated, partially unsaturated, fully unsaturated or aromatic 4, 5, or 6 membered ring, said ring having from one to three heteroatoms that are independently selected from the group consisting of sulfur, oxygen, and nitrogen. The heterocycle may be attached at any point which affords a stable structure. Representative heterocycles include 1,3-dioxolane, 4,5-dihydro-1H-imidazole, 4,5-dihydrooxazole, furan, imidazole, imidazolidine, isothiazole, isoxazole,

morpholine, oxadiazole, oxazole, oxazolidinedione, oxazolidone, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrazole, thiadiazole, thiazole, thiophene and triazole.

The heterocycle is further optionally substituted with one to three, preferably one or two groups independently selected from halo, hydroxy, oxo, cyano, nitro, phenyl, benzyl, triazolyl, tetrazolyl, 4,5-dihydrothiazolyl, C_1-C_6 alkyl, C_1-C_4 haloalkyl, C_1-C_6 alkoxy, COR^7, $CONR^7R^7$, CO_2R^7, NR^7R^7, NR^7COR^7, $NR^7SO_2R^8$, $OCOR^8$, OCO_2R^7, $OCONR^7R^7$, SR^7, SOR^8, SO_2R^7 and $SO_2(NR^7R^7)$, where R^7 is independently at each occurrence H, C_1-C_6 alkyl, phenyl or benzyl and R^8 is independently at each occurrence C_1-C_6 alkyl, phenyl or benzyl.

The term "alkylheterocyclic" as used herein refers to an alkyl group further substitued with a heterocyclic group. Examples of alkylheterocycles include but are not limited to 2-methylimidazoline, N-methylmorpholinyl, N-methylpyrrolyl and 2-methylindolyl.

The term "basic group" refers to an organic radical which is a proton acceptor. The term "basic group" also refers to an organic group containing one or more basic radicals. Illustrative basic radicals are amidino, guanidino, amino, piperidyl, pyridyl, etc, and excludes amides.

Suitable basic radicals contain one or more nitrogen atoms and include amino, imino, amidino, N-alkylamidines, N, N'-dialkylamidines, N-arylamidines, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, amide, thioamide, benzamidino, pteridinyl, 4H-carbazolyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, or any of the preceding substituted with amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino,

trialkylamino, tetrahydroisoquinoline, dihydroisoindole, alkylideneamino, groups, or a group represented by the formula NR^1R^2.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction, that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

As used herein, the term "patient" includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals. Livestock animals are animals raised for food production. Ruminants or "cud-chewing" animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are examples of livestock. Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. Yet other examples of livestock include fish, shellfish and crustaceans raised in an aquaculture. Also included are exotic animals used in food production such as alligators, water buffalo and ratites (e.g., emu, rheas or ostriches). The preferred patient of treatment is a human.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof.

The terms "preventing", "prevention of", "prophylaxis", "prophylactic" and "prevent" are used herein interchangeably and refer to reducing the likelihood that the recipient of a compound of formula I will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term "effective amount" means an amount of a compound of formula I that is sufficient for treating or preventing a condition, or detrimental effects thereof, herein described, or an amount of a compound of formula I that is sufficient for antagonizing the MCHR1 receptor to achieve the objectives of the invention.

The term "pharmaceutically acceptable" is used herein as an adjective and means substantially non-deleterious to the recipient patient.

The term "formulation", as in pharmaceutical formulation, is intended to encompass a product comprising the active ingredient(s) (compound(s) of formula I), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the

ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutical carrier, or a compound of the formula I and a pharmaceutically acceptable co-antagonist of MCHR1 useful for the treatment and/or prevention of obesity or a related disease where antagonism of a MCH receptor may be beneficial.

The terms "diseases related to obesity" or "related diseases" as used herein refers to such symptoms, diseases or conditions caused by, exacerbated by, induced by, or adjunct to the condition of being obese. Such diseases, conditions and/or symptoms include but are not limited to eating disorders (bulima, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, epileptic seizure, hypertension, cerebral hemorrhage, conjestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinenamia.

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other non-human animals (as described above), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Because certain compounds of the invention contain an acidic moiety (e.g., carboxy), the compound of formula I may exist as a pharmaceutical base addition salt. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like.

Because certain compounds of the invention contain a basic moiety (e.g., amino), the compound of formula I may also exist as a pharmaceutical acid addition salt. Such salts include the salicylate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate,

hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, oxalate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and like salts. Preferred acid addition salts include the hydrochloride and oxalate salts. Acid addition salts are typically formed by reacting an equivalent amount of acid (based on moles of available basic i.e free pairs of electrons on nitrogen atoms, or a slight excess thereof) with the free base compound of the invention. The addition salt product is often isolated as the crystallization product. The crystallization may be spontaneous or may be facilitated by cooling and/or seeding. Other methods of isolating the acid addition salts are known to one of skill in the art.

Preferred Compounds of the Invention

Certain compounds of the invention are particularly interesting and preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

Preferred Ar^1

Preferred Ar^1 groups are cyclic groups selected from cycloalkyl and cycloalkene groups such as the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl. Also preferred are groups selected from tetrahydrothiophene, tetrahydrofuran, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, phenyl, tetrahydroisoxazole, piperidine, tetrahydropyridine, benzothiophene, benzofuran, naphthyl, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, each optionally substituted with C_1-C_6 alkyl, C_1-C_6 cycloalkyl, C_1-C_6 haloalkyl,hydroxy, alkoxyalkyl, cyano, halo, aryl, carboxamide, and C_1-C_6 carboxyalkyl. More preferred Ar^1 groups include cycloalkyl, cycloalkenyl, substituted or unsubstituted phenyl, benzothiophene, benzofuran and naphthyl.

Preferred L^1 groups

Preferred as L^1 are groups having between 3 to 8 carbon atoms in the main chain. Also preferred are L^1 groups selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-SCH_2-$, $-OCH_2-$, $-CH_2SCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2SCH_2-$, $-OCH_2CH_2OCH_2-$, $-O(CH_2)_3SCH_2-$, $-OCH(Et)CH_2CH_2SCH_2$, $-OCH(iPr)CH_2CH_2SCH_2$, $-OCH(CH_3)CH_2CH_2SCH_2$,$-O(CH_2)_3SCH(CH_3)-$, $-O(CH_2)_2SCH(CF_3)-$, $-OCH_2CH(NO_2)SCH_2-$, $-OCH(CN)CH_2SCH_2$, $-OCH_2CH(NH_2)SCH_2-$, $-CH_2O(CH_2)_3CH_2O-$, and $-CH_2O(CH_2)_2CH_3O-$

Preferred X_2 group

Also preferred is an L^1 group having the formula X_2-$(CR^3R^4)_m$-X_3 wherein a preferred X_2 group is selected from O, S, and $-NR^6$, and wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, benzyl, C_1-C_8 alkylamine, and aryl.

Preferred X_3 Groups

Also preferred is an L^1 group wherein, when L^1 is X_2-$(CR^3R^4)_m$-X_3; wherein X_3 is a group selected from $-OCH_2$, $-SCH_2$, $-NR^6C(O)CH_2$, $-NHCH_2$, wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, benzyl, and aryl. More preferred is an X_3 group selected from $-OCH_2$, and $-SCH_2$.

Also preferred is a compound of formula I wherein L^1 is X_2-$(CR^3R^4)_m$-X_3, and wherein the chain between X_2 and X_3 i.e., $-(CR^3R^4)_m-$ is an alkyl chain of 3 to 8 carbon atoms, or an alkenyl chain of 3 to 8 carbon atoms and optionally contains an alkyl, phenyl, amino, or cycloalkyl group as a side chain.

Preferred Ar^2 Groups

A preferred Ar^2 group is a 5-member monocyclic aromatic heterocyclic group having 1, 2, or 3 heteroatoms selected from oxygen, sulfur, and nitrogen. More preferred is a heterocyclic group selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, 2-pyraziline, pyrazolidine, isoxazole, isothiazole, 1,3,4-oxadiazole, 1,2,3-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole. Most preferred Ar^2 are the oxadiazolyl or oxazolyl groups, and positional isomers thereof.

Preferred Ar^3 Groups

Preferred Ar^3 group is a 6-member carbocyclic or heterocyclic group having 0, 1, 2, or 3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and optionally substituted with one to two groups. More preferred is a cyclic group selected from phenyl, pyran, piperidine, pyridine, pyridazine, and piperazine. Most preferred Ar^3 is phenyl.

Preferred L^2 groups

Preferred L^2 groups include a divalent group having between 3 and 8 atoms in the main cahin. Also preferred are L^2 groups selected from the group consisting of –OCH_2CH_2-, -$O(CH_2)_3$-, -CH_2, -CH_2CH_2, -$CH_2CH_2CH_2$, -CH=CH, -CH_2CH_2CH=CH- and X_4-$(CR^3R^4)_m$-X_5.

Preferred X_4 Groups

Preferred X_4 groups include divalent groups, radicals, or fragments of the formula –C(O)NR^6 wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, benzyl, C_1-C_8 alkylamine, and aryl.

Also preferred is an X_4 group selected from O, S, -$NR^6C(O)NR^6$, -C(S)NR^6, $NR^6C(S)NR^6$, $NR^6C(NR^6)NR^6$, -NR^6SO_2-, wherein R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, benzyl, C_1-C_8 alkylamine, and aryl.

Preferred X_5 Groups

Preferred is an X_5 group selected from -OCH_2, -SCH_2, O, -NR^6C(O), -NR^6C(S), -C(O)NR^6, -C(S)NR^6, $NR^6C(S)NR^6$, NC(NR^6)N, $NR^6C(O)NR^6$, -NR^6SO_2 wherein R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, benzyl, C_1-C_8 alkylamine, and aryl. More preferred is an X_5 group selected from –OCH_2, SCH_2 and O.

Also preferred is a compound of formula I wherein the chain between X_4 and X_5 is preferably an alkyl chain of 2 to 8 carbon atoms, or an alkenyl chain of 2 to 8 carbon atoms and optionally containing an alkyl, phenyl, or cycloalkyl group as a side chain.

Preferred Q groups:

The substituent Q of formula I is a basic group. A basic group is an organic group containing one or more basic radicals. Preferred Q groups are those represented by the formula $-NR^1R^2$

Preferred R^1 and R^2 Groups

Preferred R^1 and R^2 groups are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 alkylcycloalkyl, phenyl, benzyl, COR^9, SO_2R^9, and $(CH_2)_nSO_2R^6$.

Also preferred are R^1 and R^2 groups which combine with each other, the nitrogen atom to which they are attached to form a heterocycle selected from morpholino, thiomorpholino, pyrrole, 2H-pyrrole, 2-pyrroline, pyrrolidine, oxazole, thiazole, imidazoline, imidazolidine, pyrazole, pyrazoline, piperazinyl, piperadinyl, pyrazinyl, pyrimidine each optionally substituted with a C_1-C_8 alkyl group.

Also preferred is a compound of the invention having R^1 and R^2 groups wherein the R^1 and R^2 groups combine with the nitrogen atom to which they are attached and with a carbon atom one or two atoms removed from the nitrogen atom to form a cycle such as for example, azepine, diazepine, pyridine, piperidine, indolyl, N-methylpyrrolidinyl, pyrrolidinyl, morpholino, piperidinyl, and the like.

Also preferred are compounds of formula I wherein R^1 and R^2 combine together with the nitrogen atom to which they are attached to form an imine or substituted imine.

Most preferred are R_1 and R_2 which singly or in combination with each other and/or the nitrogen atom to which they are attached form the groups independently selected from methyl, ethyl, propyl, isopropyl, isobutyl, cyclopentyl, cyclohexyl, N-morpholino, azepane, diazepine, pyridine, pyrrolidine, piperidine, N-methylpiperidine, and N-methylpiperazine.

Preferred R^3 and R^4 groups:

Preferred R^3 and R^4 are independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkylene, C_2-C_8 alkynyl, phenyl, aryl, C_1-C_8 alkylaryl, $(CH_2)_nNR^5SO_2R^6$,

$(CH_2)_nC(O)R^6$, $(CH_2)_nCONR^6R^6$ and $(CH_2)_nC(O)OR^6$; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to three substitutents independently selected from oxo, nitro, cyano, C_1-C_8 alkyl, aryl, halo, hydroxy, C_1-C_8 alkoxy, C_1-C_8 halaoalkyl, $(CH_2)_nC(O)R^6$, $(CH_2)_nCONR^6R^6$ and $(CH_2)_nC(O)OR^6$.

Most preferred R^3 and R^4 substituents are independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkylene, C_2-C_8 alkynyl, phenyl, and benzyl; and wherein n is 0, or 1, and wherein R^5 is hydrogen, C_1-C_8 alkyl, phenyl or benzyl; and wherein R^6 is hydrogen, C_1-C_8 alkyl, phenyl or benzyl.

Preferred R^5 groups

A preferred R^5 group is a group independently selected from hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_5-C_8 alkylaryl, $(CH_2)_nNSO_2C_1$-C_8 alkyl, $(CH_2)_nNSO_2$phenyl, $(CH_2)_nNSO_2$aryl, -$C(O)C_1$-C_8 alkyl, -$C(O)OC_1$-C_8 alkyl; and.

Preferred R^6 groups

A preferred R^6 or $R^{6'}$ is independently selected from hydrogen, C_1-C_8 alkyl, phenyl, aryl, alkylaryl, and C_3-C_8 cycloalkyl.

An example of a preferred compound of the present invention is a compound selected from the group consisting of: 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea,

1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,

1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

1-(3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,

Cyclohexyl-ethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-morpholine,

1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane,

Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperidine,

(3-{2-Chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

1-Methyl-4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperazine,

(3-{2-Fluoro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

Cyclopentyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azocane,

Diethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine,

2-{4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-[1,3,4]oxadiazole,

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-furan-2-yl]-phenoxy}-propyl)-amine,

4-Dimethylamino-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-butyramide,

1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

1-(3-Dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-
phenyl}-urea,

Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine,

Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-amine,

2-(2-Dimethylamino-ethoxy)-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-acetamide,

Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,

1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,

Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole,

1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane,

1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane,

Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

Diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

1-(2-Dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[1,3,4]oxadiazole,

1-(5-Dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane,

Diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,

1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,

1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

(3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(5-pyrrolidin-1-yl-pent-1-enyl)-phenyl]-[1,3,4]oxadiazole,

1-(5-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-piperidine,

1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidin-4-one,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole,

Dimethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,

1-(2-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-piperidine,

1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-piperidine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole,

Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine,

Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-hex-5-enyl)-amine,

Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-but-3-enyl)-amine,

Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine,

(3-{4-[5-(Benzo[b]thiophen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

Dimethyl-(3-{4-[5-(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole,

2-[4-(3-Azetidin-1-yl-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole,

1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,

1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,

1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine,

N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-propane-1,3-diamine,

1-Methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxymethyl}-piperidine,

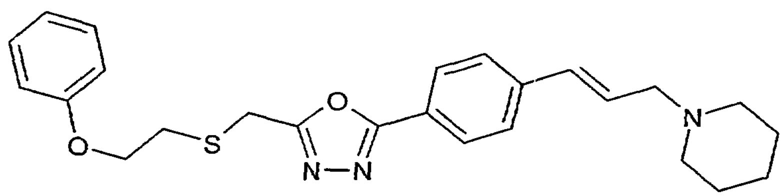
2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole,

1-(2-Diethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

5-(2-Phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole,

Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine, and pharmaceutically acceptable salts, solvates, enantiomers, diasteromers and mixture of enantiomers thereof.

A most preferred compound of the present invention is selected from the group consisting of:



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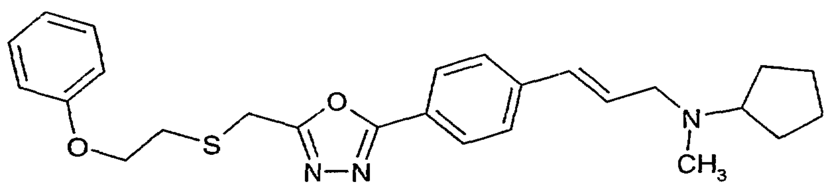

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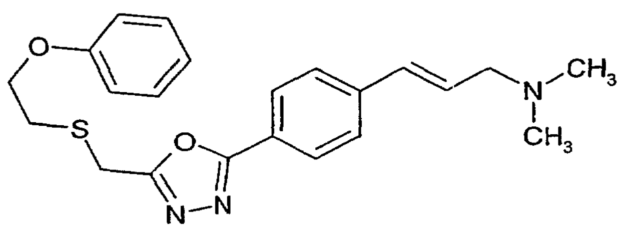

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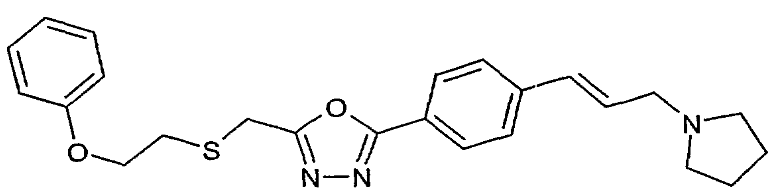

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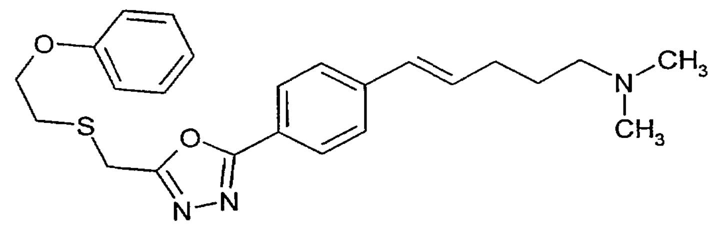

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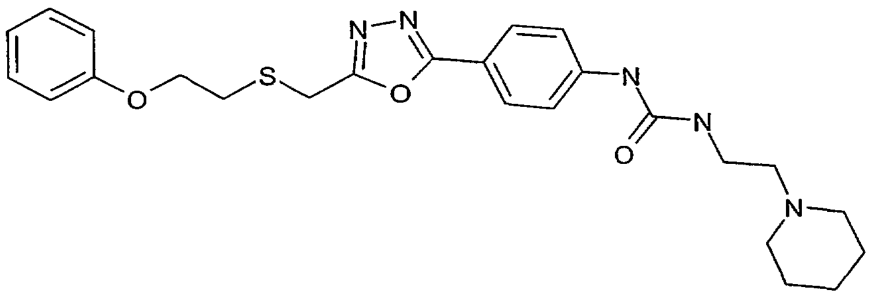

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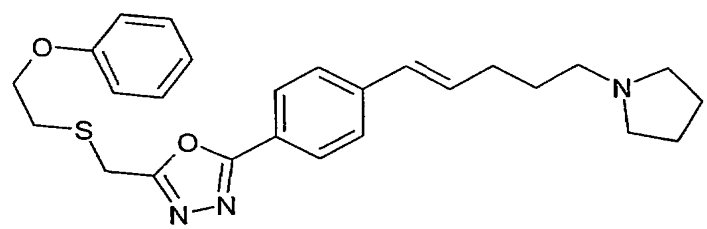

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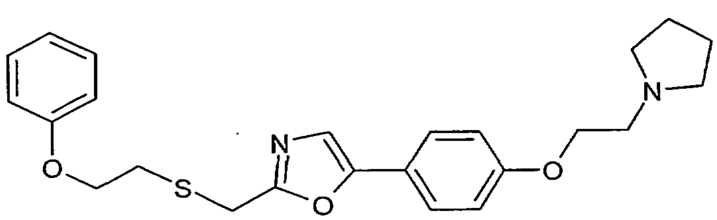

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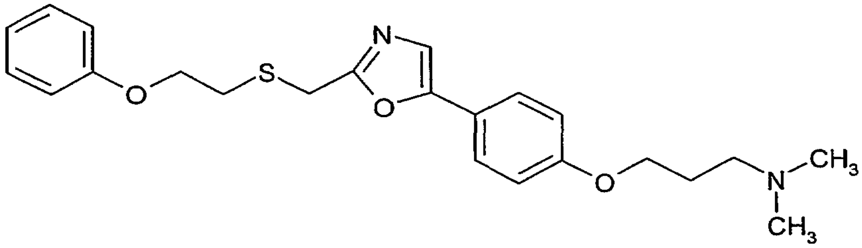

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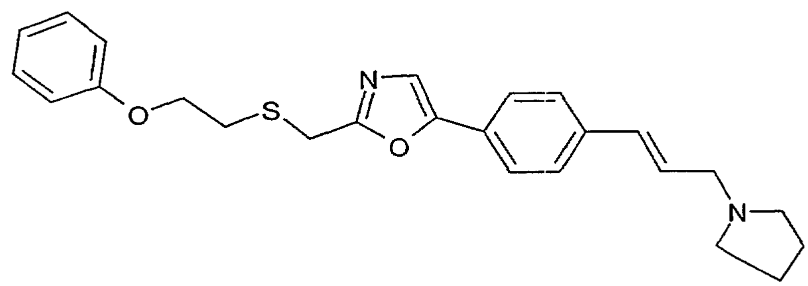
,

or a pharmaceutically acceptable salt, solvate, prodrug, enantiomer, or mixture of enantiomers thereof.

Preparing Compounds of the Invention

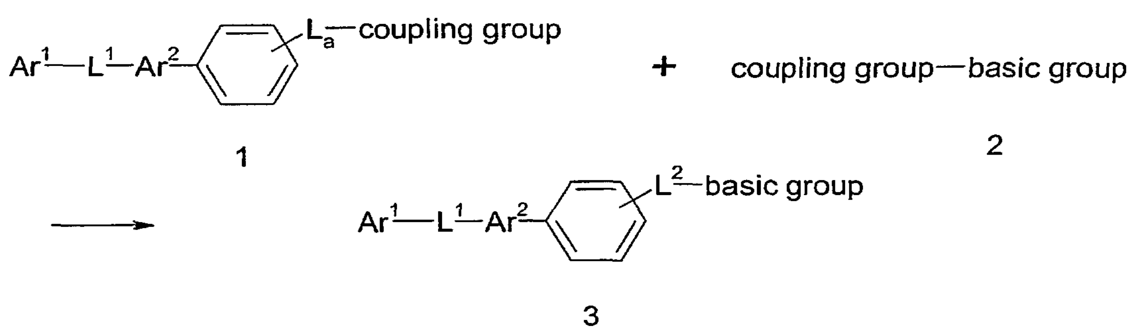
Compounds of formula I may be prepared as described in the following Schemes and Examples. Precursors to the compounds of the invention are prepared by methods known to one of skill in the art. The compounds employed as initial starting materials in the synthesis of the compounds of the invention are well known and, to the extent not commercially available, are readily synthesized by standard procedures commonly employed by those of ordinary skill in the art. More particularly, the compounds of the invention are produced in accordance with the General Methods 1 through 5 that are described in detail below, or analogous methods thereto. These reactions are often carried out in accordance with per se known methods, or analogous methods thereto. Examples of such known methods include the methods described in general reference texts such as Organic Functional Group Preparations, 2nd Edition, 1989; Comprehensive Organic Transformations, VCH Publishers Inc, 1989; Compendium of Organic Synthetic Methods, Volumes 1-10, 1974-2002, Wiley Interscience; March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, etc., and references cited therein.

General Method 1: Coupling of the basic group

The compounds of Formula 3 can be prepared by the General Method 1, described in General Scheme 1, via coupling of a compound of Formula 2 containing a basic group with a group of Formula 1, where during the course of the coupling reaction the coupling groups are retained or lost to form the linker L^2 between the basic group and the phenyl

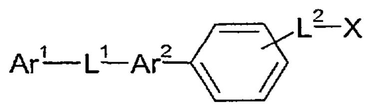
ring. Ar^1, L^1, Ar^2, L^2, and basic group are defined as above. In the schemes that follow Ar^3 of formula I has been depicted as a phenyl group for convenience only and is not intended to be limiting. Also, L_a is defined as a group that when the coupling process occurs results in the formation of the linker L^2 defined above. Furthermore, in the schemes that follow, the group L^1 is depicted by the combination of group or groups interspacing or linking the groups Ar^1 and Ar^2. Similarly, the group L^2 is depicted by the combination of group or groups interspacing or linking the groups Ar^3 and the basic group. The basic group of the compounds of the follewoing schemes in general mean the group -N(R^1R^2) unless otherwise indicated. Examples of the General Method 1 are a Displacement Process (Scheme 1a) and a Reductive Amination Process (Scheme 1b).

General Scheme 1: Coupling of Basic group



As outlined in Scheme 1a below, the coupling process of General Method 1 may consist of a displacement process whereby nucleophilic displacement of a leaving group, such as, but not limited to, halogen, triflate, tosylate, brosylate, mesylate, nosylate, nonaflate, tresylate, and the like, of Formula 4, by a nucleophilic basic group of Formula 5 affords the compounds of the invention. A leaving group is defined in one or more of the general reference texts described previously.

Scheme 1a: Displacement Process

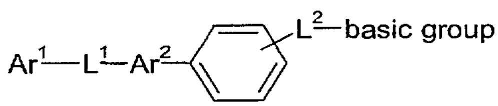


+ nucleophilic basic group ⟶

X = Leaving group (e.g., Cl, Br, I, OMs, OTs, etc)

5

4



3

One to five equivalents of the nucleophilic basic group of Formula 5 and one to five equivalents of the reactive derivative of Formula 4 may be reacted in the presence, or absence, of an inert solvent. If necessary, the reaction may be carried out in the presence of a catalytic quantity to about five equivalents of a non-interfering base. A non-interfering base is a base suitable for the intended reaction by virtue of the base not deleteriously affecting the reaction. One to two equivalents of base is normally preferable. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 24 hours.

Nucleophilic basic groups would include, but would not be limited to ammonia, primary and secondary amines, guanidines, and the like. Specific nucleophilic basic groups include ammonia, methylamine, dimethylamine, diethylamine, diisopropylamine, pyrrolidine, piperidine, morpholine, azetidine, thiomorpholine, piperazine, imidazole, and the like. Among the above nucleophilic basic groups dimethylamine, pyrrolidine, and piperidine are preferable.

If necessary, the reaction can be carried out with nucleophilic basic group synthon, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Nucleophilic basic group synthons would include, but would not be limited to, azide, phthalimide, protected amines, hexamethylenetetramine, cyanamide, cyanide anion, and the like. Following the displacement reaction, these groups would then be unmasked under standard conditions to afford the basic group. For example, displacement with potassium phthalimide followed by removal of the phthalimide group

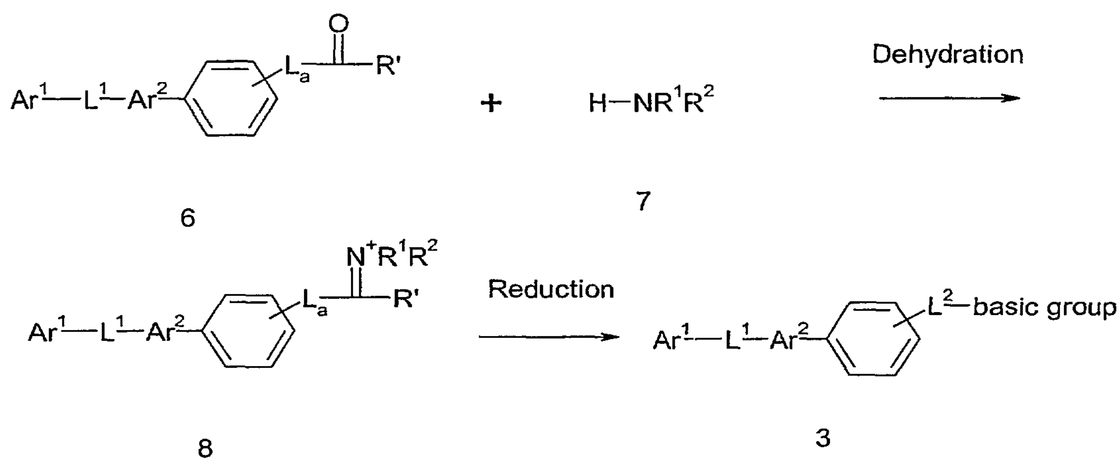
to afford the primary amine as in the Gabriel synthesis (see, March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Chapter 10, and references cited therein). Application of the synthon equivalent to the basic group applies to the processes described in all of the General Methods 1 through 5.

Examples of "inert solvent" includes amide solvents (preferably DMF or DMAC), sulfoxide solvents (preferably DMSO), sulfone solvents (preferably sulfolane or dimethylsulfone), nitrile solvents (preferably acetonitrile), halogenated hydrocarbon solvents (preferably dichloromethane), aromatic solvents (preferably toluene or benzene), ether solvents (preferably diethylether or THF), ketone solvents (preferably acetone), ester solvents (preferably ethyl acetate), alcohol solvent (preferably MeOH or EtOH), etc. Two or more of the solvents can be mixed in an appropriate ratio for use. Among the above solvents, DMF and DMSO are preferable.

Examples of "base" include, for instance, hydrides of alkali metals and alkaline earth metals (e. g., lithium hydride, sodium hydride, potassium hydride, and the like), amides of alkali metals and alkaline earth metals (e. g., sodium amide, lithium diisopropyl amide, lithium hexamethyldisilazide, and the like), alkoxides (e. g. sodium methoxide, sodium ethoxide, potassium t-butoxide, and the like), inorganic bases, such as hydroxides of alkali metals or alkaline earth metals (e. g., sodium hydroxide, lithium hydroxide, potassium hydroxide, and the like), carbonates and hydrogen carbonates of alkali metals or alkaline earth metals (e. g., potassium carbonate, sodium bicarbonate, sodium carbonate, cesium carbonate, and the like), amine bases (such as, N-methylmorpholine, DBU, DBN, pyridine, 2,6-lutidine, triethylamine, diisopropylethylamine, and the like). Among the above bases, sodium hydride, potassium carbonate, and cesium carbonate are preferable.

As outlined in Scheme 1b below, the coupling process can consist of a Reductive Amination Process. A compound of Formula 6 is condensed with ammonia, or a primary, or secondary amine under dehydration / reduction conditions. Scheme 1b is a process analogous to that described in for example, Chem Pharm Bull 1999, 47 (8), 1154-1156; Synlett 1999, (11), 1781-1783; and J Med Chem 1999, 42 (26), 5402-5414 and references cited therein.

Scheme 1b: Reductive Amination Process



The carbonyl compound of Formula 6 is reacted with an amine of Formula 7 in an inert solvent under conditions that form the iminium species of Formula 8. The iminium species is reduced *in-situ* to form the compounds of Formula 3. The reaction is normally done in the presence of a dehydrating agent and a reducing agent. Amines of Formula 7 include, but are not be limited to ammonia, primary and secondary amines, and the like. Specific amine groups include ammonia, methylamine, dimethylamine, diethylamine, diisopropylamine, pyrrolidine, piperidine, morpholine, azetidine, thiomorpholine, piperazine, imidazole, and the like. One to five equivalents of the amine group of Formula 7 and one to five equivalents of the reactive derivative of Formula 6 are reacted in the presence, or absence, of an inert solvent. The use of an excess of dehydrating agent is normally preferable. The reaction is carried out in the presence of one to hundred equivalents of a reducing agent. One to three equivalents of reducing agent is preferable. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 24 hours. For the above amination reaction, MeOH and EtOH are preferable as inert solvents.

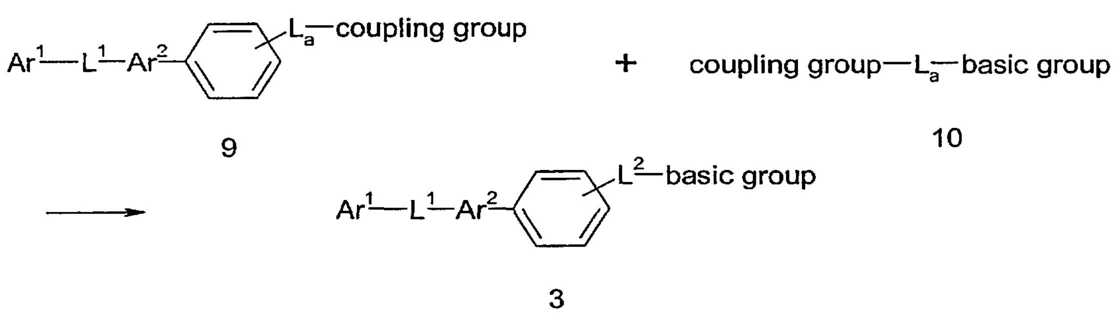
Examples of "dehydrating agents" may be anhydrous molecular sieves beads, anhydrous molecular sieve pellets, powdered anhydrous molecular sieves, anhydrous molecular sieves on supports (such as zeolite), anhydrous magnesium sulfate, anhydrous sodium sulfate, and the like. Among the above dehydrating agents, anhydrous molecular sieves pellets and powdered anhydrous molecular sieves are preferable.

Examples of "reducing agents" include hydrogen gas or hydrogen gas precursor and a hydrogenation catalyst. Other "reducing agents" include sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, sodium borohydride/Ti (O*i*-Pr)4, borohydride-exchange resin, and the like. Examples of "hydrogen gas precursors" include formic acid, 1,4-cyclohexadiene, and the like. Examples of "hydrogenation catalyst" include palladium on carbon, platinum on carbon, rhodium, ruthenium, nickel and the like. The metal can be used as a finely dispersed solid or absorbed on a support, such as carbon or alumina. Among the above reducing agents, sodium cyanoborohydride and sodium triacetoxyborohydride are preferred.

General Method 2: Coupling of the linker group

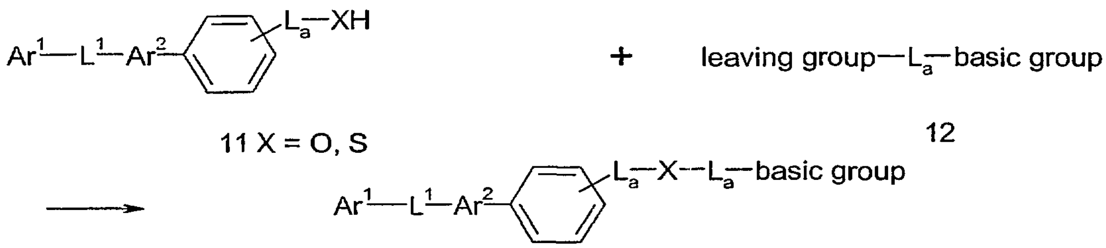
The compounds of Formula 3 can be prepared by the General Method 2, described in General Scheme 2, via reaction of the coupling group of Formula 9 with a coupling group of Formula 10.

General Scheme 2



Examples of the General Method 2 are an Ether/Thioether Alkylation Process (Scheme 2a), an Acylation/Sulfonylation Process (Scheme 2b), Urea/Thiourea/Guanidine Coupling Process (Scheme 2c1, 2c2, 2c3), an Organometallic Process (Scheme 2d), and a Wittig-type Coupling (Scheme 2e). As outlined in Scheme 2a below, the coupling process of General Method 2 can consist of a Ether/Thioether Alkylation Process. Nucleophilic displacement by an alcohol or thiol-containing compound of Formula 11 (or Formula 11') with a compound of Formula 12 (or Formula 12') containing a leaving group affords the ether and thioether compounds of Formula 13. Scheme 2a is a process analogous to that described in The Chemistry of the Ether Linkage; Patai, Wiley, 1967, 446, 460; and in March's Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5th Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001, Chapter 10.

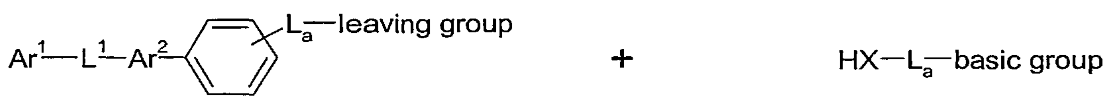
Scheme 2a: Ether/Thioether alkylation process



11 X = O, S

12

13 X = O, S



11'

12' X = O, N

One to five equivalents of the alcohol or thiol of Formula 11 (or Formula 11') and one to five equivalents of the reactive derivative of Formula 12 (or Formula 12') are reacted in the presence, or absence, of an inert solvent. If necessary, the reaction can be carried out in the presence of a catalytic quantity to ten equivalents of a non-interfering base. One to three equivalents of base is normally preferable. The reaction is typically carried out between 0 °C and 120 °C. Reaction time is typically 4 to 24 hours, but may be longer depending on the particular substrate. Preferred bases for the above reaction include sodium hydride, potassium carbonate and cesium carbonate. If necessary, the reaction may be carried out with basic group synthon incorporated as the basic group in Formula 12, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the ether/thioether alkylation reaction, these groups would then be unmasked or converted under standard conditions to afford the basic group. For example, alkylation with 1-iodo-4-chloro-butane would give a 4-chlorobutane derivative of compound 11. The chloride could then be converted by the Displacement Process, described above in Scheme 1a, into the basic group of a compound of Formula 13. Among the inert solvents, DMF and DMSO are preferable.

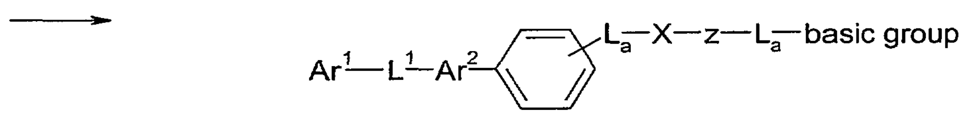
As outlined in Scheme 2b below, the coupling process of General Method 2 can consist of a Acylation/Sulfonylation Process. Acylation or sulfonylation of an alcohol or amine compound of Formula 14 with a carboxylic acid or sulfonic acid compound of Formula 15, affords the ester, amide, sulfonic ester, or sulfonamide compounds of

Formula 16. Alternatively, acylation or sulfonylation of an alcohol or amine compound of Formula 18 with a carboxylic acid or sulfonic acid compound of Formula 17 affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 19. If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group in Formula 15 or Formula 18, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the Acylation/Sulfonylation reaction, these groups would then be unmasked or converted under standard conditions to afford the basic group.

Scheme 2b: Acylation/sulfonylation process

14 X = OH, NHR

15 Z = HO_2C, HO_3S

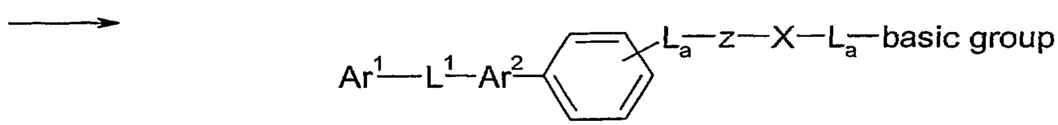


16 X = O, NR; Z = C=O, SO_2

or,

17 X = CO_2H, SO_3H

18



19 X = O, NR; Z = C=O, SO_2

The carboxylic acid (or sulfonic acid) residue of compound 15 (or compound 17) is activated for coupling as a "reactive acylating agent." "Reactive acylating agents" are described in detail in Advanced Organic Chemistry, 4th Edition, Part B, Reactions and

Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapter 3, and references cited therein. The "reactive acylating agent" can be formed and isolated, then reacted with the compound of Formula 14 (or 18), or formed *in situ* and reacted with the compound of Formula 14 (or 18), to form the compound of Formula 16 (or 19).

One to five equivalents of the "reactive acylating agent" of compound 15 (or compound 17) and one to five equivalents of compound of Formula 14 (or 18) are reacted in an inert solvent. If necessary the reaction may be carried out in the presence of one to five equivalents of 1-hydroxybenzotriazole, 1-hydroxy-7-azabenzotriazole, and (or) a catalytic quantity to five equivalents of a base. The reaction is normally carried out between 0 °C and 120 °C. Reaction time is normally 4 to 48 hours.

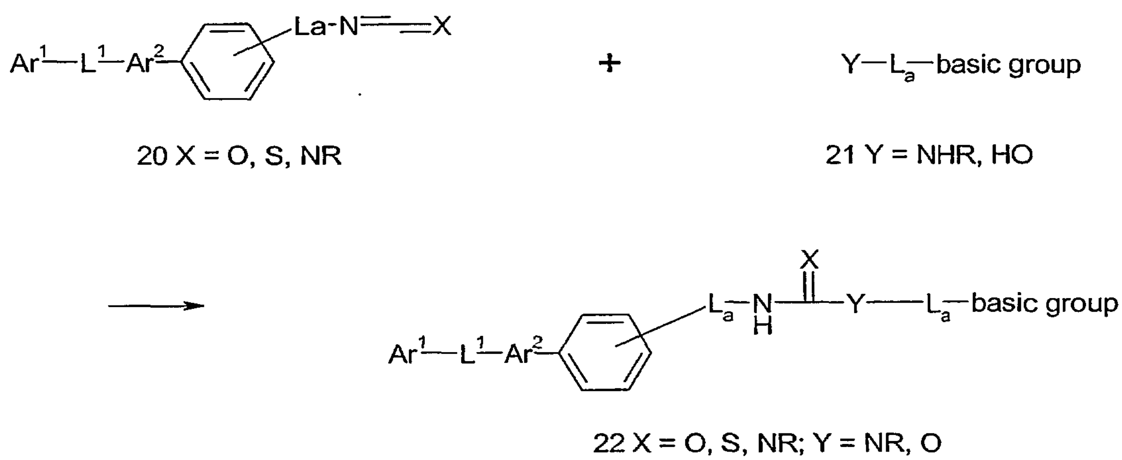
Examples of "reactive acylating agent" of compound 15 (or compound 17) include acid halides (e.g., acid chloride, acid bromide, and the like), mixed acid anhydrides (e. g., acid anhydrides with C_1-C_6 alkyl-carboxylic acid, C_6-C_{10} aryl-carboxylic acid, and the like), activated esters (e. g., esters with phenol which may have substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 1-hydroxy-7-azabenzotriazole, and the like), thioesters (such as, 2-pyridinethiol, 2-imidazolethiol, and the like), N-acylimidazoles (e.g., imidazole, and the like), etc.

A "reactive acylation agent" may also be formed reacting the carboxylic acid (or sulfonic acid) residue of compound 15 (or compound 17) with a dehydration/condensation agent. Examples of a "dehydration/condensation agent" include dicyclohexylcarbodimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodimide (EDCI), (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and the like. Preferred solvents for the above reaction include acetonitrile, THF, and dichloromethane.

Preferred bases for the above reaction include triethylamine, pyridine, and dimethylaminopyridine are preferable.

As outlined in Scheme 2c1, Scheme 2c2, and Scheme 2c3 below, the coupling process of General Method 2 can consist of a Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process. The processes described are analogous to that described in US Patents 5,849,769 and 5,593,993, and references cited therein.

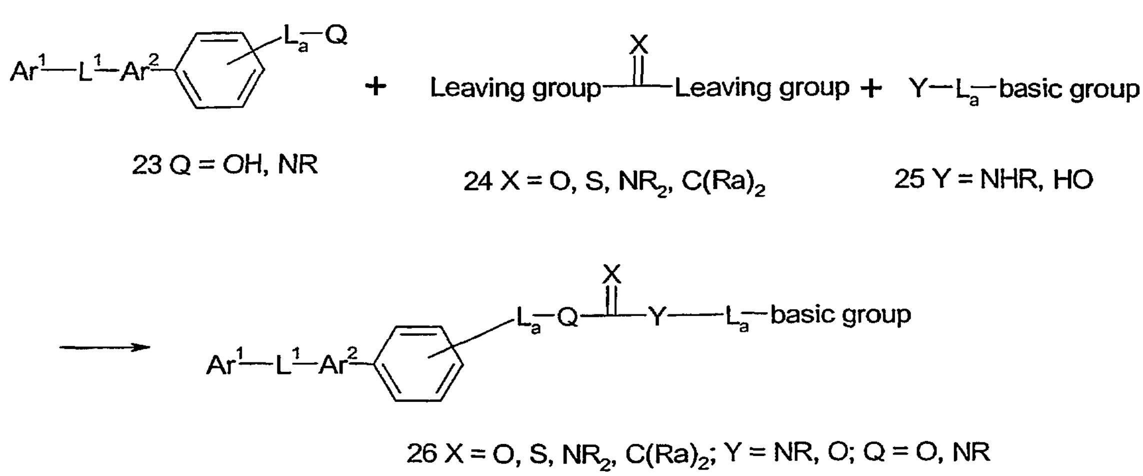
Scheme 2c1: Urea/Thiourea/Guanidine/Carbamate-Type coupling



One to five equivalents of the isocyanate, isothiocyanate, carbodiimide of Formula 20 and one to five equivalents of compound of Formula 21 are reacted in an inert solvent. The reaction is typically carried out between 0 °C and 150 °C. Preferred reaction time is between 4 to 48 hours. Preferred solvents for the above reaction include acetonitrile, DMF, DMSO, THF, and dichloromethane.

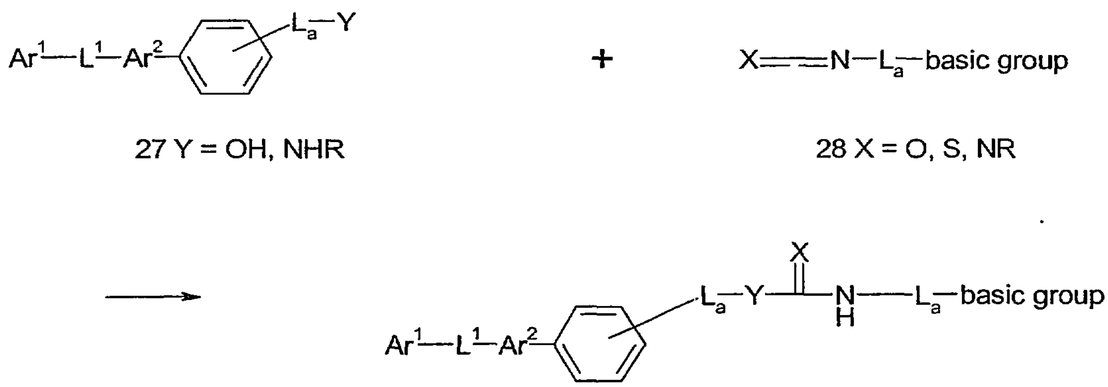
If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group wherein a synthon is as described ealier. Following the Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process, these groups would then be unmasked or converted under standard conditions to afford the basic group.

Scheme 2c2: Urea/Thiourea/Guanidine/Carbamate-Type coupling



Approximately one equivalent of the compound of Formula 23 and one equivalent of compound of Formula 24 and one equivalent of the compound of Formula 25 are reacted in an inert solvent. The reaction is typically carried out between 0 °C and 150 °C. Reaction time is normally 4 to 48 hours. The sequence of addition depends upon the reactivity of the individual reagents. The intermediate addition product may be isolated and subsequently be condensed with the second reagent. The reaction may or may not require the addition of a catalyst. Prefered solvents for the above reaction include acetonitrile, DMF, DMSO, THF, toluene, isopropanol, and dichloromethane. Acids and bases as described previously may be used to catalyze the above reaction.

Scheme 2c1: Urea/Thiourea/Guanidine/Carbamate-Type coupling

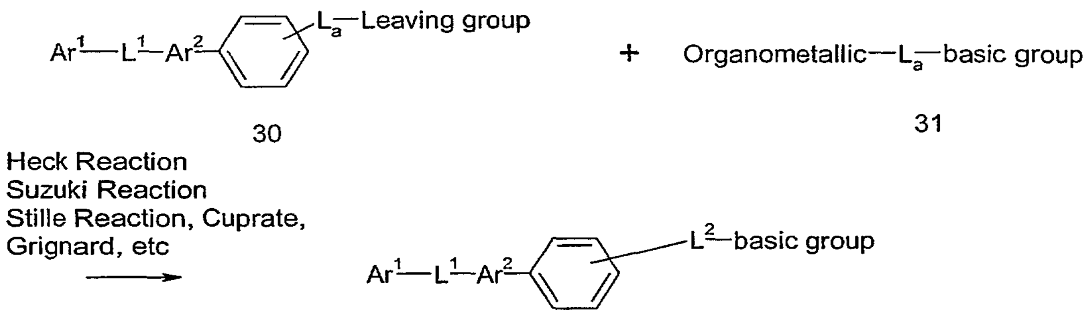


29 X = O, S, NR_2; Y = NR, O

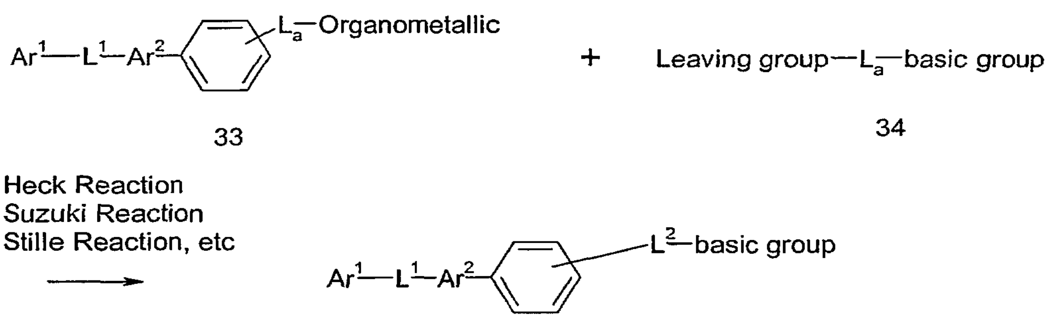
One to five equivalents of the isocyanate, isothiocyanate, carbodiimide of Formula 28 and one to five equivalents of compound of Formula 27 are reacted in an inert solvent. The reaction is normally carried out between 0 °C and 150 °C. Reaction time is normally 4 to 48 hours.

As outlined in Schemes 2d below, the coupling process of General Method 2 may consist of a Organometallic Coupling Process.

Scheme 2d: Organometallic Coupling Process



30 31 32



33 34 32

The compound of Formula 30 (or Formula 34) is coupled with an organometallic compound of Formula 31 (or Formula 33) (containing a basic group, or basic group precursor) in an Organometallic Coupling Process to afford the compounds of the invention of Formula 32.

"Organometallic Coupling Processes" include "palladium-catalyzed cross coupling reactions," such as, Heck-type coupling reactions, Suzuki-type coupling reactions and Stille-type coupling reactions. Other organometallic coupling reactions include, organocuprate coupling reactions, Grignard coupling reactions, and the like. A general description of Organometallic Coupling is given in detail in Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapters 7 and 8, and references cited therein.

In Scheme 2d. the compound of Formula 30 (or Formula 34) is coupled with the organometallic reagent of Formula 31 (orFormula 33) in the presence, or absence, of a transition metal catalyst, and/or a phosphine or arsine, and/or a base in an inert solvent. Other additives, such as, copper salts, silver salts, and the like may be added. Approximately one equivalent of the compound of Formula 30 (or Formula 34) is reacted

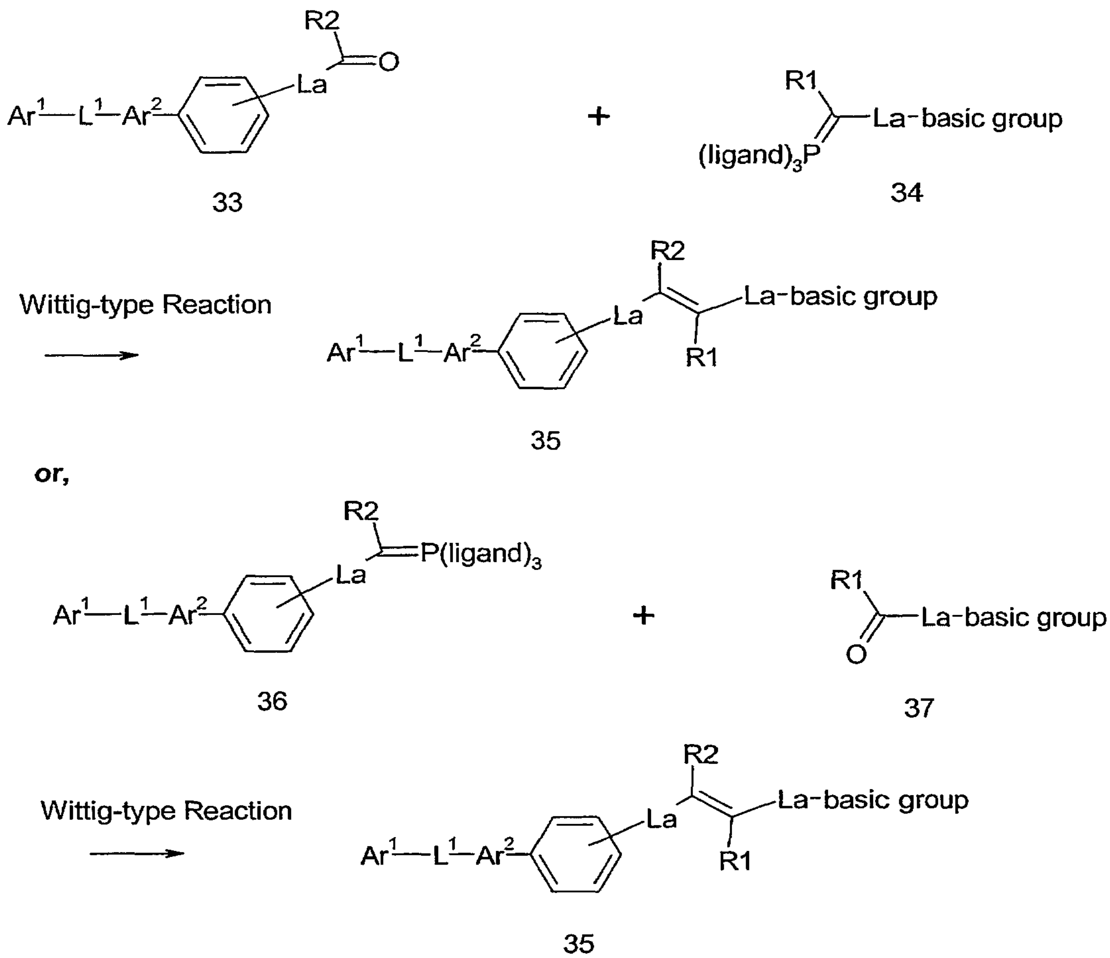
with one to five equivalents of the compound of Formula 31 (or Formula 33) with the appropriate additives in an inert solvent. The reaction is normally carried out between –78 °C and 200 °C for between 4 to 72 hours.

Examples of "organometallic reagents" include, organomagnesium, organozinc, mixed organocuprate, organostannane, or organoboron compounds, and the like. Examples of "transition metal catalysts" include, palladium and nickel catalysts, such as, $Pd(OAc)_2$, Pd $(PPh_3)_4$, $PdCl_2$, $Pd(PPh_3)Cl_2$, $Pd(OCOCF_3)_2$, $(CH_3C_4H_5P)_2PdCl_2$, $[(CH_3CH_2)_3P]_2PdCl_2$, $[(C_6H_{11})_3P]_2PdCl_2$, $[(C_6H_5)_3P]_2PdBr_2$, $Ni(PPh_3)_4$, $(C_6H_4CH{=}CHCOCH{=}CHC_6H_5)_3Pd$, and the like. Among the above transition metal catalysts, $Pd(OAc)_2$, $Ni(PPh_3)_4$, and $Pd(PPh_3)_4$ are preferable.

Examples of "phosphines or arsines" include, a trialkyl or triarylphosphine or arsine, such as triisopropylphosphine, triethylphosphine, tricyclopentylphosphine, triphenylphosphine, triphenylarsine, 2-furylphosphine, tri-o-tolylphosphine, tricyclohexylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 2-(Di-t-butylphosphino)biphenyl, and the like. Among the above "phosphines and arsines," tri-o-tolylphosphine, triphenylarsine, and tricyclohexylphosphine are preferable.

Examples of "other additives" include, copper salts, zinc salts, lithium salts, ammonium salts and the like. Among the above "other additives," CuI, LiCl, and $n\text{-}Bu_4N^+Cl^-$ are preferable. If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group as described previously. As outlined in Schemes 2e below, the coupling process of General Method 2 can consist of a Wittig-type Coupling Process. The compound of Formula 33 (or Formula 37) is coupled with the phosphorus ylene (or ylide) reagent of Formula 34 (or Formula 36) to afford the compounds of Formula 35 of the invention. A general description of Wittig-type Coupling Reactions is given in detail in general reference texts such as Advanced Organic Chemistry, 4th Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, Chapter 2, and references cited therein.

Scheme 2e: Wittig-type couplings

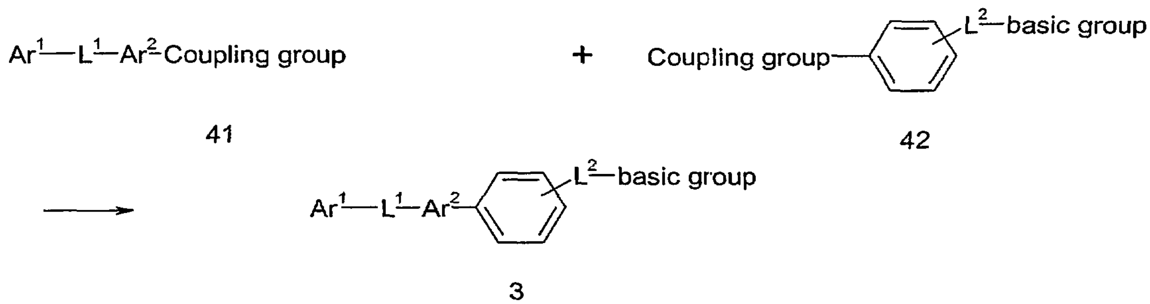


The compound of Formula 33 (or Formula 37) is coupled with the phosphorus ylene (or ylide) reagent of Formula 34 (or Formula 36) in the presence, or absence, a base in an inert solvent to form the compounds of the invention of Formula 35. Other additives, such as, lithium salts, sodium salts, potassium salts, and the like may be added. Approximately one to five equivalents of the compound of Formula 33 (or Formula 37) is reacted with one to five equivalents of the compound of Formula 34 (or Formula 36) with the appropriate additives an inert solvent. The reaction is normally carried out between – 78 °C and 120 °C for between 2 to 72 hours. The Wittig reaction product may be reduced to form other compounds of the invention using reducing agents known to one of skill in the art and/or described previously. Preferred bases for the above organometallic reactions include, sodium hydride, DBU, potassium t-butoxide, and lithium hexamethyldisilazide.

General Method 3: Coupling of the five-membered ring heterocycle and phenyl groups

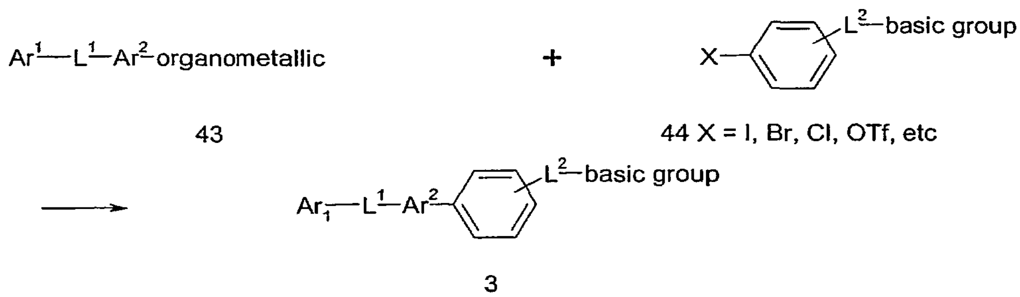
The compounds of Formula 3 can be prepared by the General Method 3, described in General Scheme 3, via coupling of the compounds of Formula 38 with a compound of Formula 39. An example of the General Method 3 is a Aryl Coupling Process (Scheme 3a). The aryl-coupling reaction is carried out in accordance with per se known methods, or analogous methods thereto, such as those described in the general reference texts discussed previously.

General Scheme 3: Aryl-coupling process

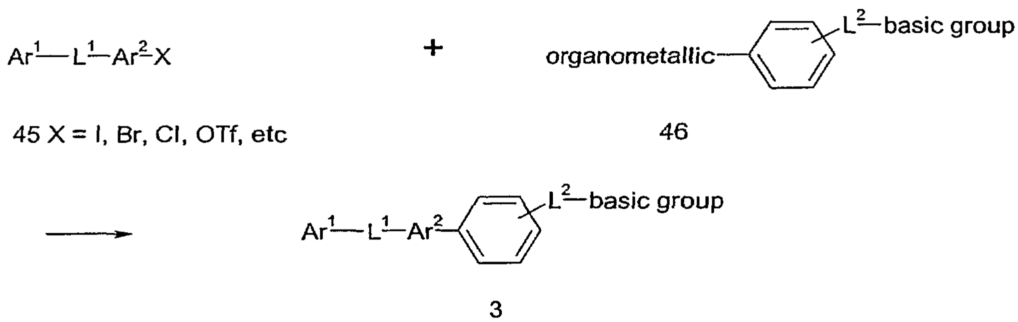


The compound of Formula 44 (or Formula 45) is coupled with an organometallic compound of Formula 43 (or Formula 46) in an Aryl Coupling Process to afford the compounds of the invention of Formula 3.

General Scheme 3a: Aryl Coupling



or,



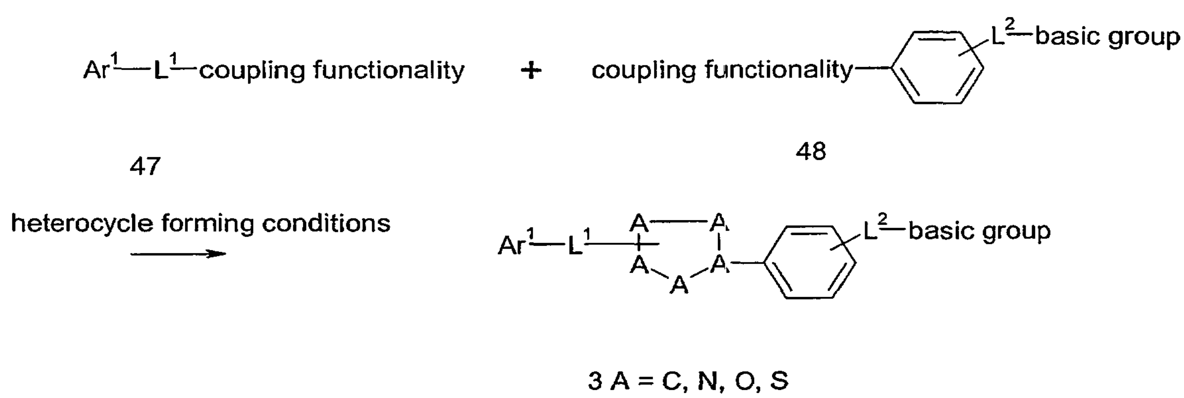
The compound of Formula 44 (or Formula 45) is coupled with the organometallic reagent of Formula 43 (Formula 46) in the presence, or absence, of a transition metal catalyst, and (or) a phosphine or arsine, and (or) a base in an inert solvent. Other additives, such as, copper salts, silver salts, and the like may be added. Approximately one equivalent of the compound of Formula 44 (or Formula 45) is reacted with one to five equivalents of the compound of Formula 43 (Formula 46) with the appropriate additives an inert solvent. The reaction is normally carried out between –78 °C and 200 °C for between 4 to 72 hours. Examples of "organometallic reagents", "transition metal catalysts" "phosphines or arsines" "other additives" and "base" have been described previously.

General Method 4: Heterocycle Formation

The compounds of Formula 3 can be prepared by the General Method 4, described in General Scheme 4, via reaction of the compound of Formula 47 containing a coupling group with a compound of Formula 48 containing a coupling group, where during the course of the coupling reaction the coupling groups form the 5-membered ring heterocycle between the linker L^1 and the phenyl ring. Ar^1, L^1, Ar^2, L^2, and basic group are defined as above. Examples of heterocyclic ring forming reactions are given in

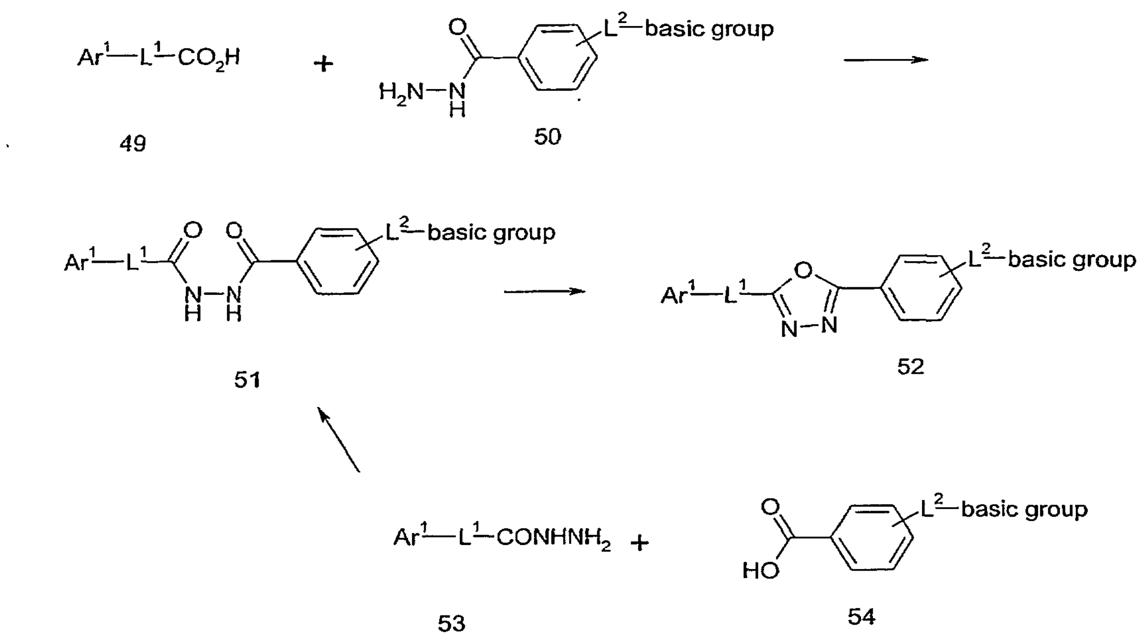
Comprehensive Heterocyclic Chemistry, Volumes 1-8, A. P. Katritzky and C. W. Rees Eds, Pergamon Press, 1984; Heterocyclic Chemistry, 3rd Ed, Thomas L. Gilchrist, Addison-Wesley-Longman Ltd, 1997; An Introduction to the Chemistry of Heterocyclic Compounds, 3rd Ed, R. M. Acheson, Wiley Interscience, 1976; etc, and references cited therein. Specific examples of the General Method 4 include an Oxadiazole Process (Schemes 4a and 4b), a Thiadiazole Process (Scheme 4c), and an Oxazole Process (Scheme 6 a-e). If necessary, the reaction can be carried out with a basic group synthon incorporated as the basic group, i.e., a group that could readily be converted to a basic group by methods known to one skilled in the art. Basic group synthons would include, but not be limited to, halogen, protected amine, nitrile, aldehyde, and the like. Following the Heterocycle Formation Process, these groups would then be unmasked or converted under standard conditions to afford the basic group.

General Scheme 4: Heterocycle formation



As outlined in Scheme 4a below, the coupling process of General Method 4 can consist of a Oxadiazole Process. The diacylhydrazide compound of Formula 51 is produced by acylation of an acylhydrazide of Formula 50 (or Formula 53) by a carboxylic acid derivative of Formula 49 (or Formula 54). The acylation process is carried out in accordance with the above Acylation/Sulfonylation Process of the General Method 2. The diacylhydrazide is cyclized to the oxadiazole compounds of the invention of Formula 52 utilizing dehydration processes analogous to that described in J Org Chem 1999, 64 (19), 6989-6992; and Chem Heterocycl Compd 1999, 35 (3), 275-280.

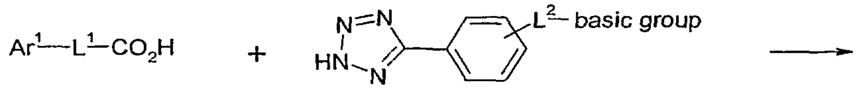
Scheme 4a: Oxadiazole Process



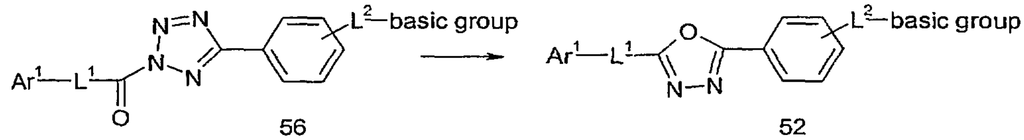
One equivalent of compound of Formula 51 is reacted with one to equivalents of a dehydrating agent in the presence, or absence, a base in an inert solvent. The reaction is normally carried out between 25 °C and 250 °C for between 4 to 72 hours. Examples of "dehydrating agents" include, $SOCl_2$, H_3PO_4, $POCl_3$, PCl_5, Tf_2O, Ac_2O, PPh_3-I_2, PPh_3-Br_2, PPh_3-Cl_2, PPh_3-CBr_4, PPh_3-CCl_4, PPA, $NH(Tms)_2$, P_2O_5, Me_2SiCl_2, $PhOPCl_2$, H_2SO_4, and the like.

As outlined in Scheme 4b below, an alternative Oxadiazole Process may be utilized to prepare the oxadiazole compounds of the invention of Formula 52. The carboxylic acid derivative of Formula 49 (or 54) is activated for coupling as a "reactive acylating agent." The acylation process is carried out in accordance with the above Acylation/Sulfonylation Process of the General Method 2. The acylated intermediate is converted to the oxadiazole compounds of the invention of Formula 52. The process is analogous to that described in Synth Commun 1994, 24 (11), 1575-1582; J Org Chem 1961, 26, 2372; Synthetic Commun 24(11),1575-1582 (1994); etc, and references cited therein.

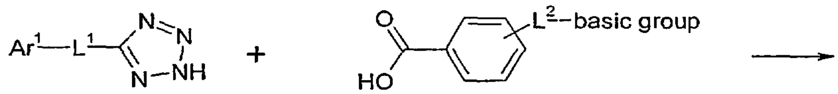
Scheme 4b: Oxadiazole Process



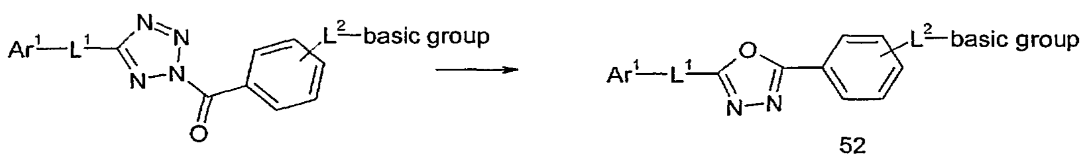
49 55



56 52



57 54

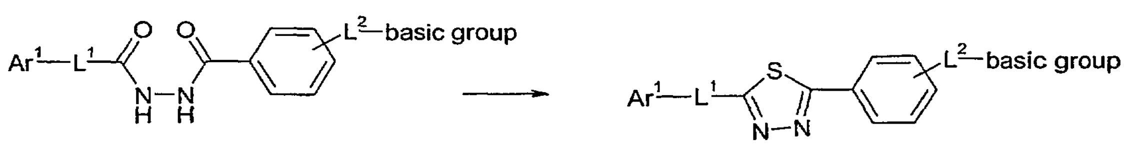


52

58

One to five equivalents of the "reactive acylating agent" of compound 49 (or compound 54) and one to five equivalents of compound of Formula 55 (or 57) are reacted in an inert solvent. If necessary the reaction can be carried out in the presence of a one to five equivalents of 1-hydroxybenzotriazole, 1-hydroxy-7-azabenzotriazole, and (or) a catalytic quantity to five equivalents of a base. The reaction intermediate of Formula 56 (or 58) may, or may not, be isolated. The reaction is normally carried out between 0 °C and 200 °C. Reaction time is normally 4 to 48 hours. Reactive acylation agents have been discussed and may similarly be prepared for compounds 49 and/or 55 as described previously.

Scheme 4c: Thiadiazole Process



51 59

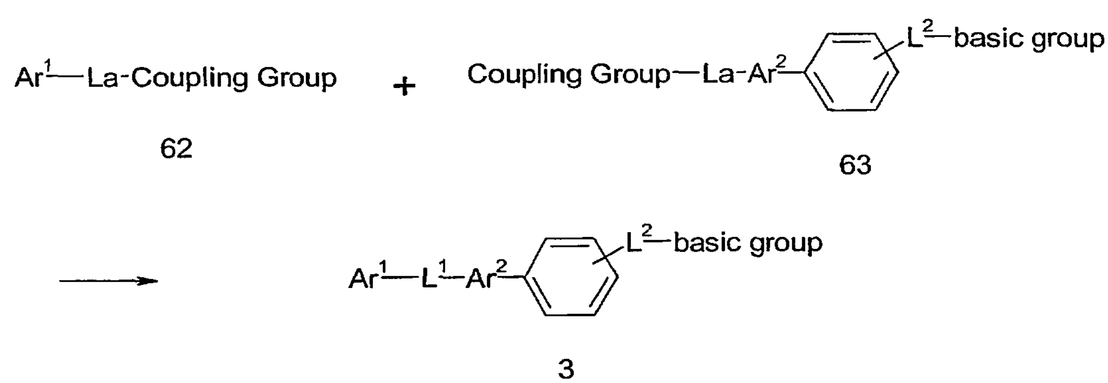
One equivalent of compound of Formula 51 is reacted with one to five equivalents of a thiol dehydrating agent in the presence, or absence, a base in an inert solvent. The reaction is normally carried out between 25 °C and 250 °C for between 4 to 72 hours. Examples of "thiol dehydrating agents" include, P_2S_5, Lawesson reagent, and the like.

General Method 5: Coupling of the linker group L^1

The compounds of Formula 3 can be prepared by the General Method 5, described in General Scheme 5, via reaction of the coupling group of Formula 62 with a coupling group of Formula 63, where during the course of the coupling reaction the coupling groups are retained, or lost, to form the linker L^1 between the 5-membered ring heterocyclic group and Ar^1. Ar^1, L^1, Ar^2, L^2, and basic group are defined as above. La is defined as a group that when the coupling process occurs results in the formation of the linker L^2 defined above. Examples of the General Method 5 are an Ether/Thioether Alkylation Process (Scheme 5a), an Acylation/Sulfonylation Process Process (Scheme 5b), an Urea/Thiourea/Guanadine Coupling Process (Scheme 5c1, 5c2, 5c3), an Organometallic Process (Scheme 5d), and a Wittig-type Coupling (Scheme 5e).

If necessary, the reactions below may be carried out with a basic group synthon incorporated as the basic group, as described previously. Following the Coupling of the Linker Group (L^1) Process, these groups would then be unmasked or converted under standard conditions to afford the basic group.

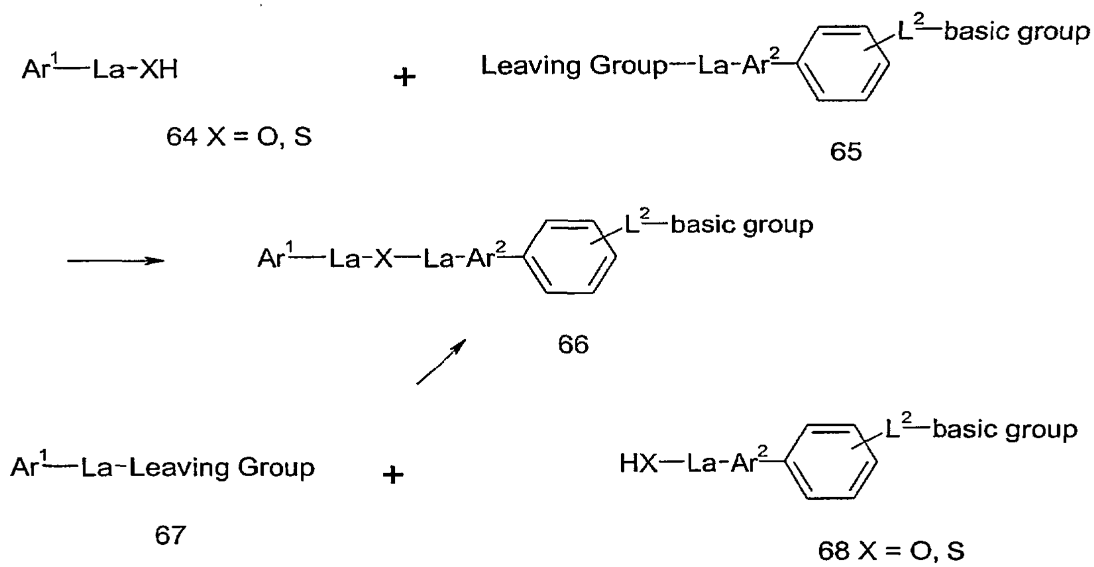
General Scheme 5: Coupling of Linker Group L_1



As outlined in Scheme 5a below, the coupling process of General Method 5 can consist of a Ether/Thioether Alkylation Process. Nucleophilic displacement by an alcohol or thiol-containing compound of Formula 64 (or Formula 68) with a compound of

Formula 65 (or Formula 67) containing a leaving group affords the ether and thioether compounds of Formula 66 of the invention. The processes are analogous to the process described for the General Method 2, described in Scheme 2a, and carried out in accordance with the above method.

Scheme 5a: Ether/Thioether alkylation process



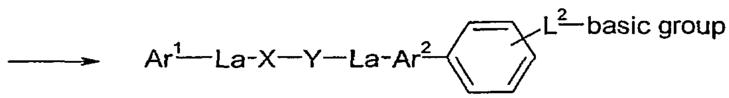
As outlined in Scheme 5b below, the coupling process of General Method 5 can consist of an Acylation/Sulfonylation Process. Acylation or sulfonylation of an alcohol or amine compound of Formula 70 with a carboxylic acid or sulfonic acid compound of Formula 69, affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 71. Alternatively, acylation or sulfonylation of an alcohol or amine compound of Formula 72 with a carboxylic acid or sulfonic acid compound of Formula 73 affords the ester, amide, sulfonic ester, or sulfonamide compounds of Formula 74.

The processes are analogous to the process described for the General Method 2, described in Scheme 2b, is carried out in accordance with the above method.

Scheme 5b: Acylation/Sulfonylation Process

69 $X = CO_2H, SO_3H$

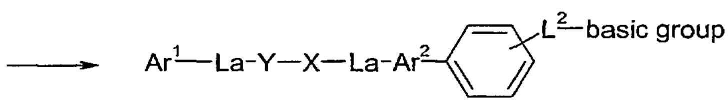
70 Y = NHR, O



71 X = CO, SO_2; Y = NR, O

72 Y = NHR, O

73 $X = CO_2H, SO_3H$



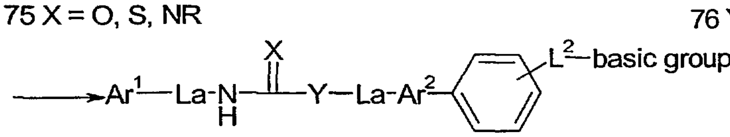
74 X = CO, SO_2; Y = NR, O

As outlined in Schemes 5c1, 5c2, and 5c3, below, the coupling process of General Method 5 can consist of a Urea/Thiourea/Guanidine/Carbamate-Type Coupling Process to afford the compounds of Formula 77, 81, and 84 of the invention. The processes are analogous to the processes described for the General Method 2, described in Schemes 2c1, 2c2, and 2c3, are carried out in accordance with the above method.

Scheme 5c1: Urea/Thiourea/Guadinine/Carbamate-Type Coupling

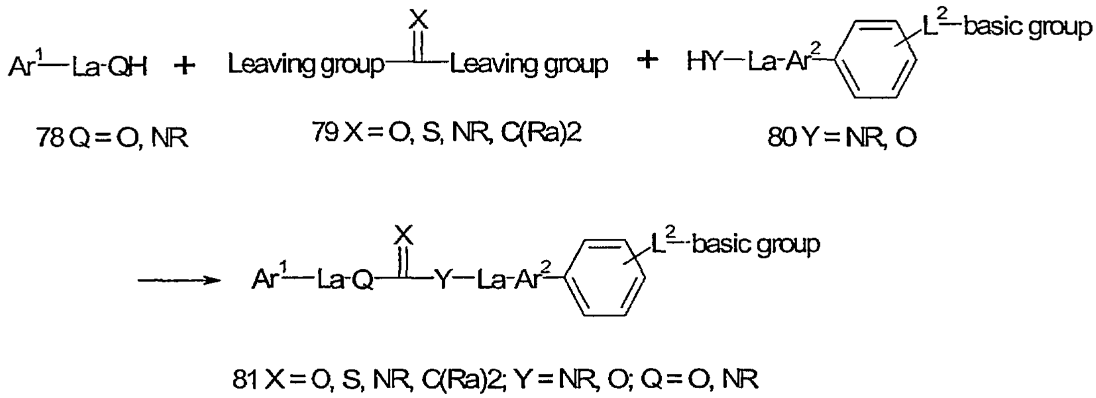
75 X = O, S, NR

76 Y = NR, O

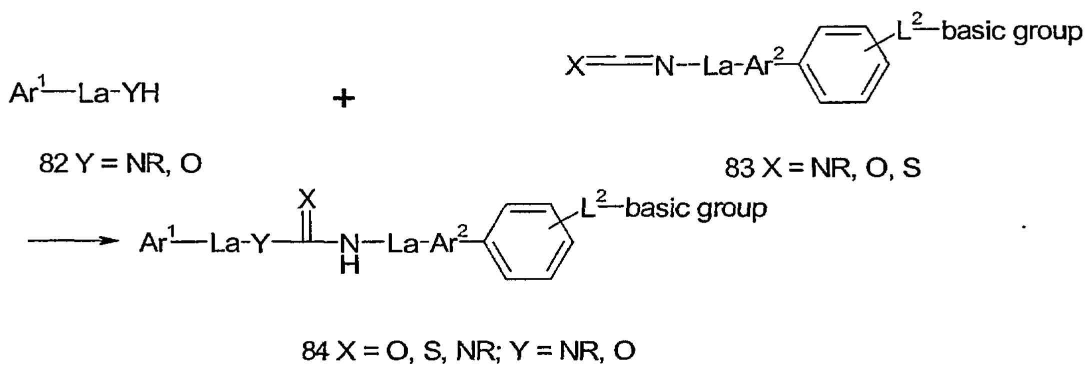


77 X = O, S, NR; Y = NR, O

Scheme 5c2: Urea/Thiourea/Guadinine/Carbamate-Type Coupling

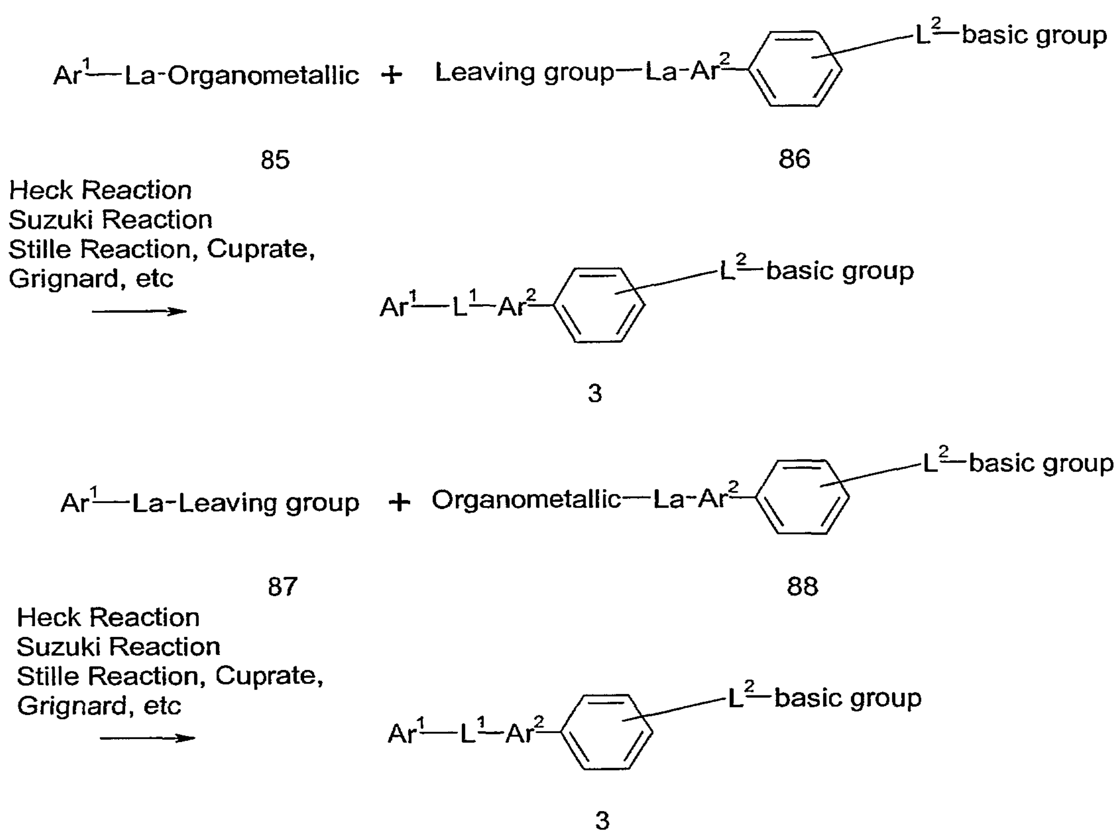


Scheme 5c3: Urea/Thiourea/Guadinine/Carbamate-Type Coupling



As outlined in Schemes 5d below, the coupling process of General Method 5 can consist of a Organometallic Coupling Process. The compound of Formula 86 (or Formula 87) is coupled with an organometallic compound of Formula 85 (or Formula 88) in an Organometallic Coupling Process to afford the compounds of Formula 3 of the invention. The processes are analogous to the processes described for the General Method 2, described in Scheme 2d, and are carried out in accordance with the above methods.

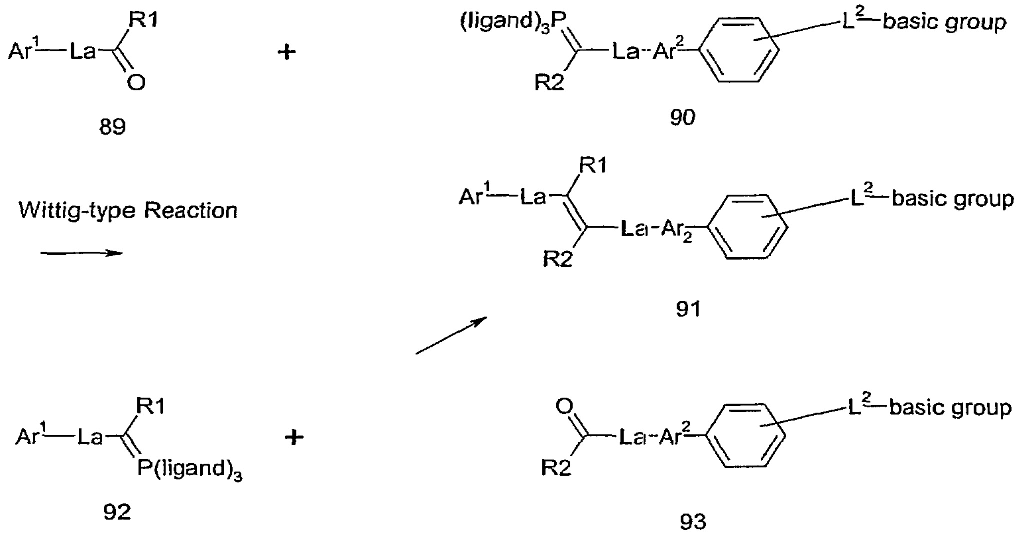
Scheme 5d: Organometallic Coupling Process



85 86 3 87 88 3

As outlined in Schemes 5e below, the coupling process of General Method 2 can consist of a Wittig-type Coupling Process. The compound of Formula 89 (or Formula 93) is coupled with the phosphorus ylene (or ylide) reagent of Formula 90 (Formula 92) to afford the compounds of Formula 91 of the invention. The processes are analogous to the processes described for the General Method 2, described in Scheme 2e, and are carried out in accordance with the above methods.

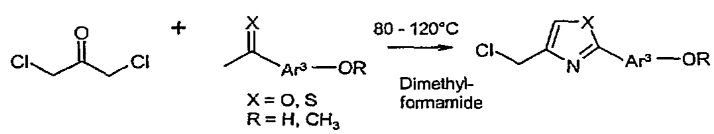
Scheme 5e: Wittig-type couplings



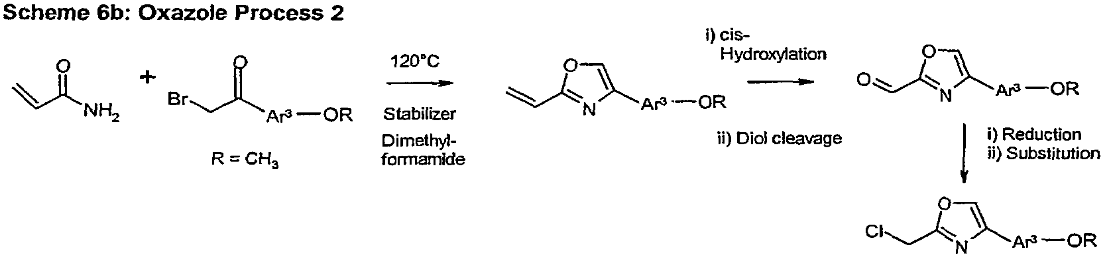
Preparation of Oxazole and Oxathiazole compounds

As outlined in schemes 6a-c (below) the formation of oxazoles and thiazoles require elevated temperatures from 80 – 120°C in solvents like dimethylformamide (scheme 6a + b) or phosphoryl chloride (scheme 6c).

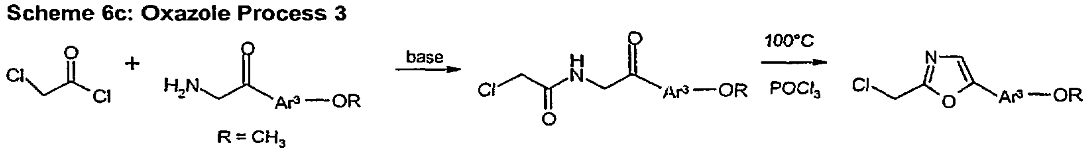
Scheme 6a: Oxazole and Thiazole Process 1



Scheme 6b: Oxazole Process 2



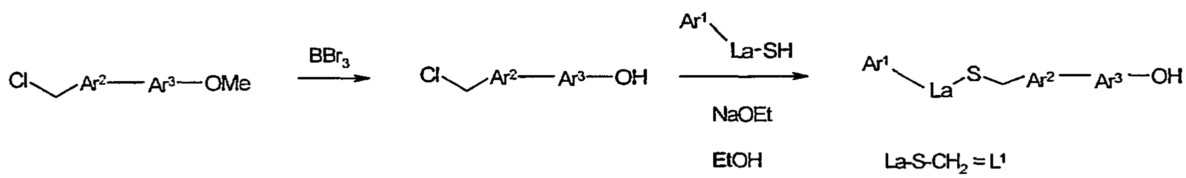
Scheme 6c: Oxazole Process 3



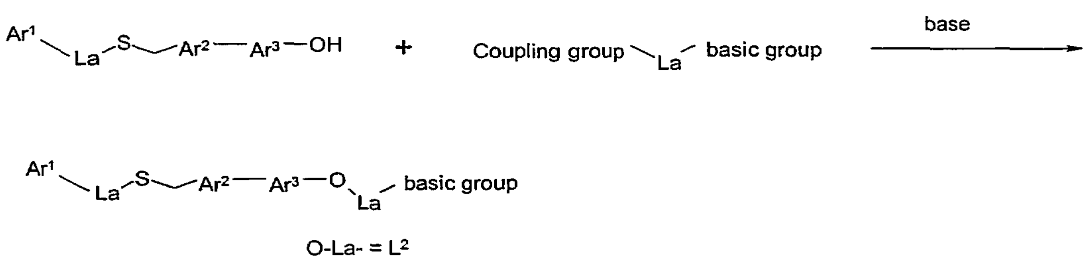
These heterocyclic cyclisations result either in chloromethyl substituted oxazoles and thiazoles (scheme 6 a + c) or in vinyl substituted oxazole (scheme 6b). After cis-hydroxylation of the later vinyl substituted oxazole, followed by diol cleavage, as known to the artesian, the resulting formyl substituted oxazole can be converted via reduction

and substitution to the chloro methyl substituted oxazole (scheme 6b). The cyclisation of □-bromoketone with acrylamide (scheme 6b) is preferably performed in the presence of a stabiliser (such as 2,6 di-tert.-butyl-4-methyl-phenol) to prevent polymerisation of the acrylamide. As outlined in scheme 6c, the condensation of 2-chloro acetyl chloride with an □-aminoketone in presence of a base such as, for example, triethylamine, affords a product in high yield that can be cyclised in phosphoryl chloride to result in formation of an oxazole. Unlike general scheme 4, these heterocyclic formations of oxazoles and thiazoles do not work as desired in the presence of Ar^1-L^1- nor in the presence of -L^2-basic group, so that these groups have to be introduced later, as outlines in schemes 6d and 6e.

Scheme 6d: Formation of the Linker Group L_1



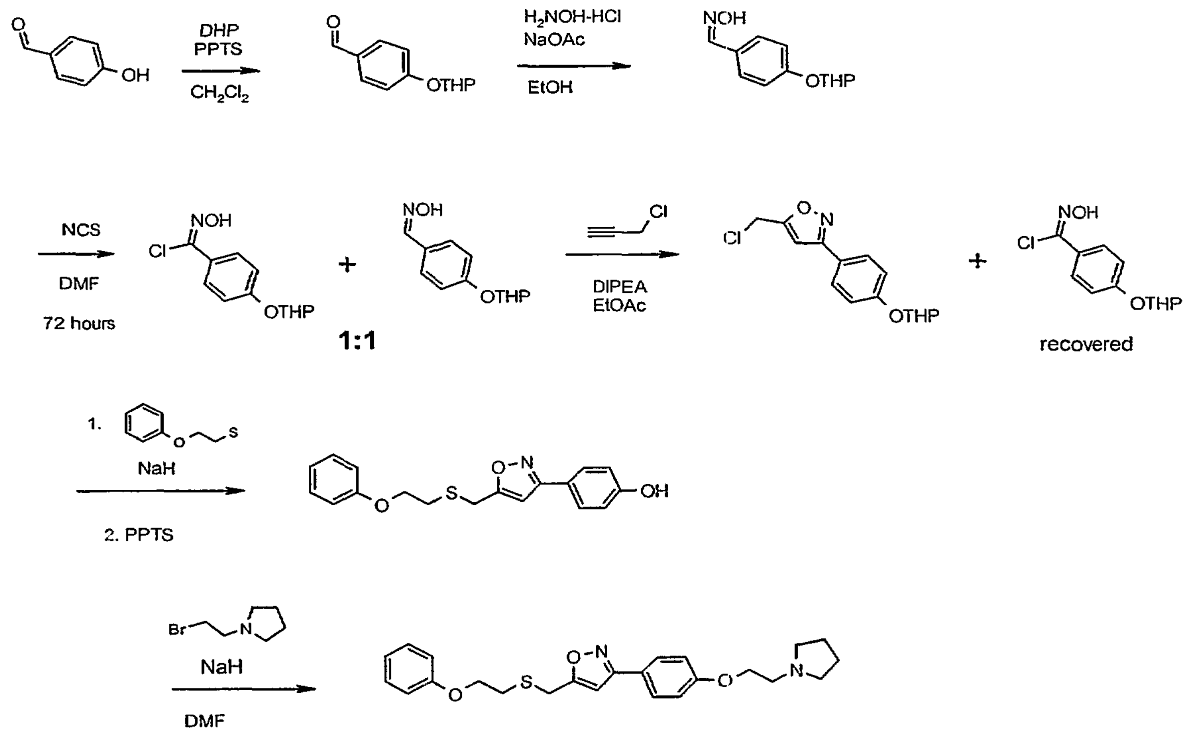
Scheme 6e: Formation of the Linker Group L_2



In order to achieve formation of the linker L^1, the chloromethyl substituted oxazoles or thiazoles from scheme 6a-c can be used as alkylation substrates for thiolates (scheme 6d). Therefore, a thiol is treated with a base, like sodium ethoxide in ethanol, before addition of the chloro methyl substituted oxazole. This alkylation proceeds in the presence of an unprotected phenol. The unprotected phenol can be incorporated into linker L^2 in a subsequent reaction, as outlined in scheme 6e in solvents such as dimethylformamide and involving bases such as potassium carbonate. As outlined in scheme 6d, the phenol may be obtained from the Lewis-acid mediated cleavage of a methylether with Lewis-acids, preferably, borontribromide in solvents such as dichloromethane.

For compounds wherein Ar^2 is oxazole, positional isomers of the oxazole group (e.g isoxazole) may be made as shown in Scheme 7.

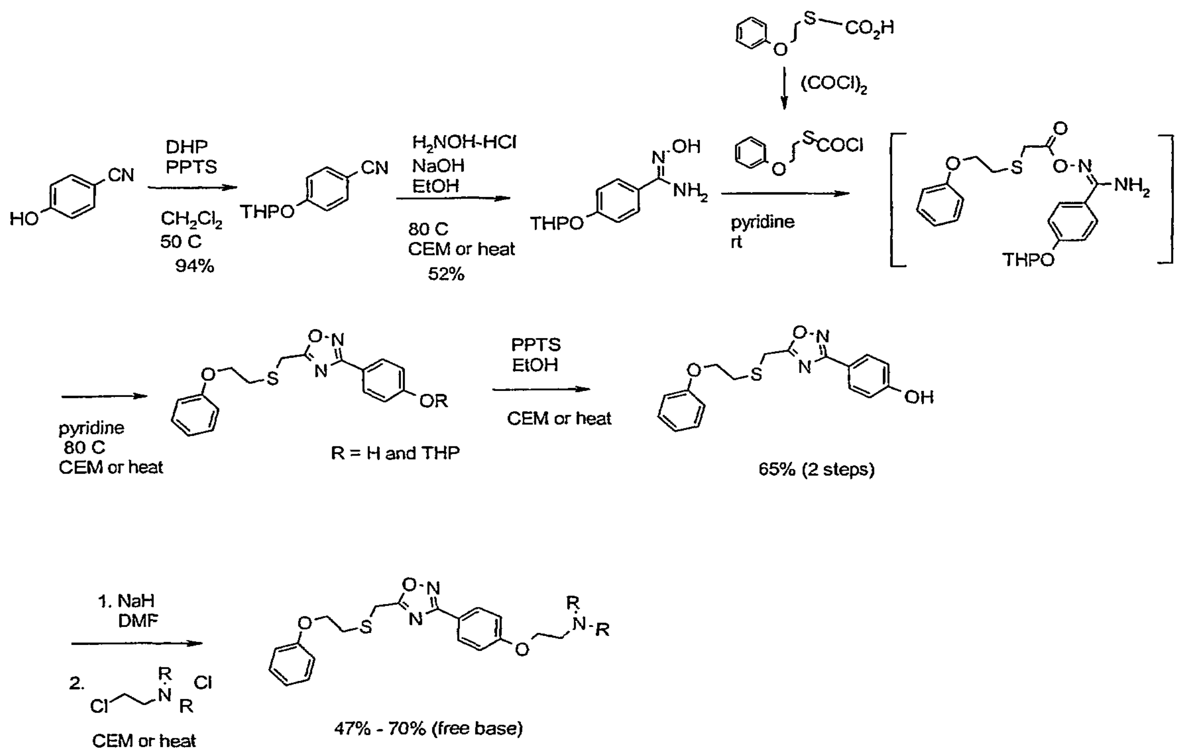
Scheme 7



4-Hydroxy-benzaldehyde is protected as the tetrahydropyran (THP) ether, using dihydropyran and p-toluenesulfonic acid (PPTS) in dichloromethane. The aldehyde functionality is converted to an oxime with hydroxylamine hydrochloride and sodium acetate in ethanol. The oxime is then converted to a chloro-oxime with NCS in DMF. Dipolar cycloaddition of the chloro-oxime and 3-chloropropyne in ethyl acetate using DIPEA as catalyst gives the intermediate 5-chloromethyl-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole. This is then used to alkylate 2-phenoxy-ethanethiol. This intermediate is deprotected with PPTS to give 4-[5-(2-phenoxy-ethylsulfanylmethyl)-isoxazol-3-yl]-phenol. The phenol is alkyated with 1-(2-chloro-ethyl)-pyrrolidine hydrochloride to give the final product, 5-(2-phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-isoxazole.

The 1,2,4-oxadiazole simer may be prepared following the procedure of Scheme as shown in Scheme 8 for the particular example.

Scheme 8



As shown, 4-Cyanophenol is protected as the Tetrahydropyran (THP) ether using dihyropyran and dihydropyran and p-toluenesulfonic acid (PPTS) in dichloromethane. The cyano functionality is converted to an amidoxime functionality by reaction with hydroxylamine hydrochloride and NaOH in ethanol in a microwave chamber at 80 C. A mixture of the amidoxime and (2-phenoxy-ethylsulfanyl)-acetyl chloride in pyridine is microwaved at 80 C to give the isoxazole intermediate as a mixture of protected THP ether and deprotected phenol. After removal of pyridine under vacuum, the reaction products are treated with PPTS in ethanol and microwaved at 75 C to deprotect any remaining THP ether, giving 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenol. The phenol is alkyated with 1-(2-chloro-ethyl)-pyrrolidine hydrochloride to give the final product, 5-(2-phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole hydrochloride.

One of skill in the art is aware that other compounds within the scope of the invention may be made as shown or by modifications to the procedures provided which are not cumbersome and are known to one of skill in the art or accessible in the general reference

texts or literature available to one of skill in the art. Futhermore, in addition to the discussive procedures herein, detailed examples are provided which would further assist one of skill in the art to make the appropriate modifications to arrive at compounds within the scope that are not specifically exemplified.

Demonstration of Function

In order to demonstrate that compounds of the present invention have the capacity to bind to and inhibit the function of MCHR1, binding and functional assays were established. All ligands, radioligands, solvents and reagents employed in these assays are readily available from commercial sources or can be readily prepared by those skilled in the art.

The full-length cDNA for human MCHR1 was cloned from a human adult brain cDNA library (Edge Biosystems, Cat. 38356) by standard polymerase chain reaction (PCR) methodology employing the following primers: sense, 5'-GCCACCATGGACCT GGAAGCCTCGCTGC-3'; anti-sense, 5'-TGGTGCCCTGACTTGGAGGTGTGC-3'. The PCR reaction was performed in a final volume of 50 μl containing 5 μl of a 10x stock solution of PCR buffer, 1 μl of 10 mM dNTP mixture (200 μM final), 2 μl of 50 mM $Mg(SO_4)$ (2 mM final), 0.5 μl of 20 μM solutions of each primer (0.2 μM final), 5 μl of template cDNA containing 0.5 ng DNA, 0.5 μl of Platinum Taq High Fidelity DNA polymerase (Gibco Life Technologies) and 36 μl of H_2O. PCR amplification was performed on a Perkin Elmer 9600 thermocycler. After denaturation for 90 sec at 94°C, the amplification sequence consisting of 94 °C for 25 sec, 55 °C for 25 sec and 72 °C for 2 min was repeated 30 times, followed by a final elongation step at 72 °C for 10 min. The desired PCR product (1.1 Kb) was confirmed by agarose gel electrophoresis and the band was extracted from the gel by Geneclean (Bio101) following the manufacturer's instructions. Following extraction, the cDNA fragment was cloned into pCR2.1-TOPO plasmid (Invitrogen) to confirm the identity and sequence.

In order to generate cell lines stably expressing MCHR1, the insert was then subcloned into the Xba I and Not I sites of pcDNA(+)-3.1-neomycin (Invitrogen). After purification by Qiagen Maxi-prep kit (QIAGEN, Inc.), the plasmid was transfected by Fugene 6 (Roche Applied Science) into AV12 cells that had been previously transfected with the promiscuous G protein $G_{\alpha 15}$. The transfected cells were selected by

G418 (800 μg/ml) for 10-14 days and single colonies were isolated from culture plates. The G418-resistant colonies were further selected for MCHR1 expression by measuring MCH-stimulated Ca^{2+} transients with a fluorometric imaging plate reader (FLIPR, Molecular Devices).

Typically, individual clones are plated out in 96-well plates at 60,000 cells per well in 100 μl of growth medium (Dulbecco's modified Eagle's medium (DMEM), 5% fetal bovine serum, 2 mM L-glutamine, 10 mM HEPES, 1 mM sodium pyruvate, 0.5 mg/ml Zeocin, and 0.5 mg/ml Geneticin). After 24 hrs at 37°C, medium is removed and replaced with 50 μl of dye loading buffer (Hank's balanced salt solution (HBSS) containing 25 mM HEPES, 0.04% Pluronate 127 and 8 μM Fluo3 Both from Molecular Probes)). After a 60 min loading period at room temperature, dye loading buffer is aspirated and replaced with 100 μl of HEPES/HBBS. Plate is placed in FLIPR and basal readings are taken for 10 sec, at which point 100 μl of buffer containing 2 μM MCH (1 μM final) is added and measurements are taken over 105 sec. To correct for variations between clones in numbers of cells per well, the MCH response is normalized to the response induced by epinephrine.

Both the ^{125}I-MCH binding and functional GTPγ^{35}S binding assays employed membranes isolated from a clone designated as clone 43. Typically, cells from 20 confluent T225 flasks were processed by washing the monolayers in cold phosphate-buffered saline (PBS), scraping the cells into same and re-suspending the cell pellet in 35 ml of 250 mM Sucrose, 50 mM HEPES, pH 7.5, 1 mM $MgCl_2$, 24 μg/ml DNase I, and protease inhibitors (1 Complete® tablet, per 50 ml of buffer prepared , Roche Diagnostics). After incubation on ice for 5 min, cells were disrupted with 20-25 strokes of a Teflon/Glass homogenizer attached to an overhead motorized stirrer, and the homogenate was centrifuged at 40,000 rpm in Beckman Type 70.1 Ti rotor. The pellets were re-suspended in 250 mM Sucrose, 50 mM HEPES, pH 7.5, 1.5 mM $CaCl_2$, 1 mM $MgSO_4$ and protease inhibitors by Teflon/Glass homogenization to achieve a protein concentration of ~3-5 mg/ml (Pierce BCA assay with Bovine serum albumin as standard). Aliquots were stored at -70°C.

Binding of compounds to MCHR1 was assessed in a competitive binding assay employing ^{125}I-MCH, compound and clone 43 membranes. Briefly, assays are carried out

in 96-well Costar 3632 white opaque plates in a total volume of 200 μl containing 25 mM HEPES, pH 7.5, 10 mM $CaCl_2$, 2 mg/ml bovine serum albumin, 0.5% dimethyl sulfoxide (DMSO), 4 μg of clone 43 membranes, 100 pM ^{125}I-MCH (NEN), 1.0 mg of wheat germ agglutinin scintillation proximity assay beads (WGA-SPA beads, Amersham) and a graded dose of test compound. Non-specific binding is assessed in the presence of 1 μM unlabeled MCH. Bound ^{125}I-MCH is determined by placing sealed plates in a Microbeta Trilux (Wallac) and counting after a 5 hr delay.

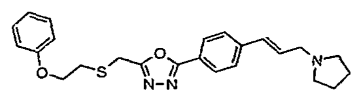
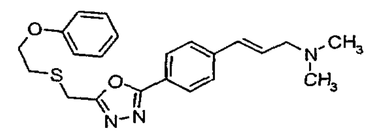
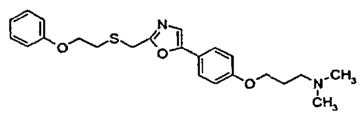
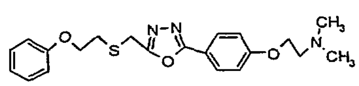
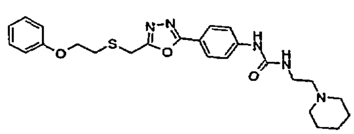
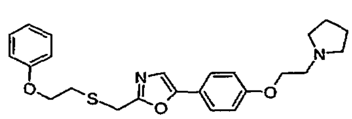
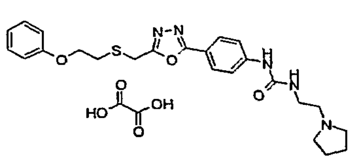
IC_{50} values (defined as the concentration of test compound required to reduce specific binding of ^{125}I-MCH by 50%) are determined by fitting the concentration-response data to a 4-parameter model (max response, min response, Hill coefficient, IC_{50}) using Excel. K_i values are calculated from IC_{50} values using the Cheng-Prusoff approximation as described by Cheng *et al.* (Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction, *Biochem. Pharmacol.*, 22: 3099-3108 (1973)). The K_d for ^{125}I-MCH is determined independently from a saturation binding isotherm.

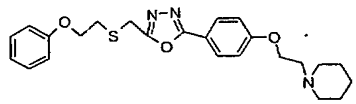
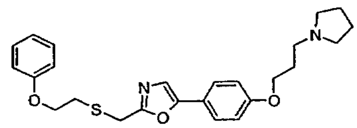
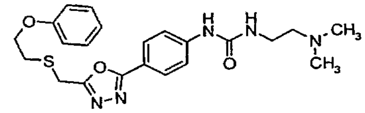
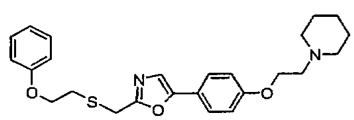
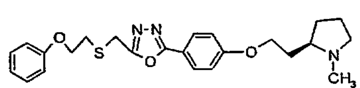
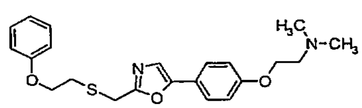
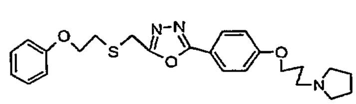
Functional antagonism of MCH activity is assessed by measuring the ability of test compound to inhibit MCH-stimulated binding of GTPγ^{35}S to clone 43 membranes. Briefly, assays are carried out in Costar 3632 white opaque plates in a total volume of 200 μl containing 25 mM Hepes, pH 7.5, 5 mM $MgCl_2$, 10 μg/ml saponin, 100 mM NaCl, 3 μM GDP, 0.3 nM GTPγ^{35}S, 40 nM MCH (approximately equal to EC_{90}), 20 μg of clone 43 membranes, 1.0 mg of wheat germ agglutinin scintillation proximity assay beads (WGA-SPA beads, Amersham) and a graded dose of test compound. The plates are sealed and left for 16-18 hrs at 4°C. After a 1 hr delay to allow plates to equilibrate to ambient temperature, bound GTPγ^{35}S is determined by counting in a Microbeta Trilux (Wallac).

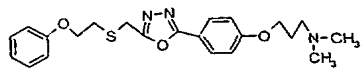
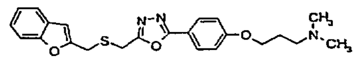
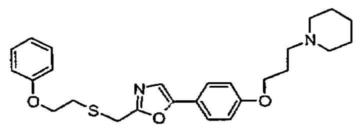
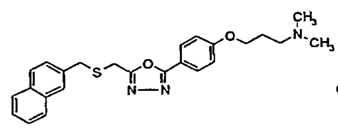
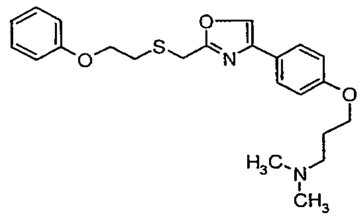
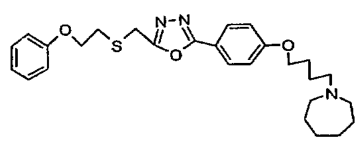
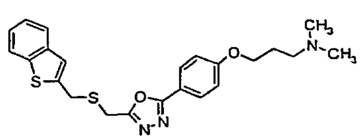
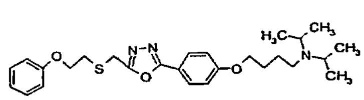
IC_{50} values (defined as the concentration of test compound required to reduce MCH-stimulated GTPγ^{35}S binding by 50%) are determined by fitting the concentration-response data to a 4-parameter model (max response, min response, Hill coefficient, IC_{50}) using Excel. K_b values are calculated from IC_{50} values using a modification of the Cheng-Prusoff approximation as described by Leff and Dougal (Further concerns over Cheng-Prusoff analysis, *Trends Pharmacol. Sci.* 14: 110-112 (1993)) after verifying competitive antagonism by Schild analysis. The EC_{50} for MCH alone is determined independently.

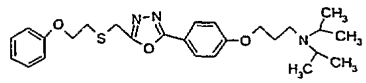
The MCHR1 binding and functional activities of 24 compounds in the oxadiazole series (tested in duplicate) are shown in Table 1

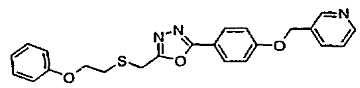
Table 1

Structure	K_i (nM)	K_b (nM)
	1.9	6.0
	3.7	11.6
	4.3	15.0
	5.3	13.6
	5.6	14.7
	5.8	12.0
	9	20.0

	9.2	19.8
	10.2	16.5
	10.4	16.2
	11.6	7.3
	12.9	39.6
	13.3	9.4
	14.3	18.1

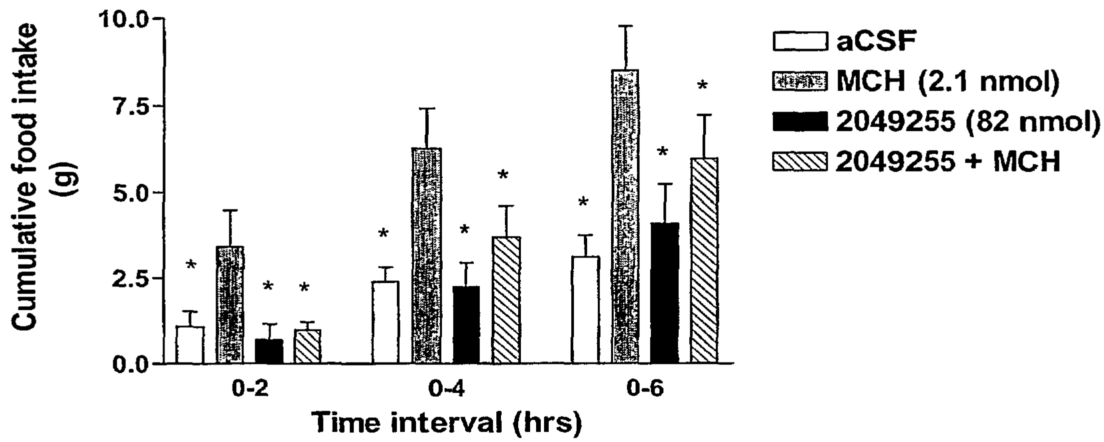
	16	11.9
 CO_2H-CO_2H	16.1	35.4
	17.9	15.9
 ClH	22.4	50.6
	35	41.5
	37.9	31.3
	48.4	139.5
	63.3	52.1

 140 145.2

 2898 6889

In order to demonstrate in vivo efficacy of this series of compounds, compound of example 136 was injected intracerebro-ventricularly in the absence or presence of 2.1 nmol MCH, and its ability to block the effect of exogenous MCH was assessed. Diet-induced obese male Long-Evans rats (Harlan, IN) weighing 500-550g at time of surgery were anesthetized with isoflurane. Stainless steel cannula guides (5mm length, 26 gauge, Plastics One, VA) were stereotaxically implanted in the lateral ventricle anteroposteriority: 0.8mm caudal to bregma; and lateral: 1.5mm from midline suture. Animals were individually housed in a temperature regulated room (24°C) with a reverse 12 hour light/dark cycle (dark 10:00/22:00). Water and food (Teklad 95217, Harlan, WI) were available ad libitum. After surgery, animals were allowed to recover 7 days before experimental use. On test day, food was removed 1 hr prior to testing and animals (4 groups, n = 6 per group) were injected between 0900 and 1000 with 5μl of vehicle (artificial CSF), 2.1 nmol MCH, 82 nmol of compound of example 136, and MCH plus compound of example 136. Cumulative food intake was measured at 2, 4 and 6 hours after injection. The results are shown in Fig. 1. Treatment with compound of example 136 completely blocked the orexigenic effect of exogenous MCH (* $p < 0.05$ vs. MCH alone).

Fig.1



Utility

As antagonists of the MCHR1binding, a compound of the present invention is useful in treating conditions in human and non-human animals in which the the MCHR1 receptor has been demonstrated to play a role. The diseases, disorders or conditions for which compounds of the present invention are useful in treating or preventing include, but are not limited to, diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, atherosclerosis of coronary, cerebrovascular and peripheral arteries, gastrointestinal disorders including peptid ulcer, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, neurogenic inflammation of airways, including cough, asthma, depression, prostate diseases such as benign prostate hyperplasia, irritable bowel syndrome and other disorders needing decreased gut motility, diabetic retinopathy, neuropathic bladder dysfunction, elevated intraocular pressure and glaucoma and non-specific diarrhea dumping syndrome. By inhibiting the MCH activity the compounds of the invention provide anorexic effects. That is, the compounds of the invention are useful as appetite suppressants and/or weightloss agents. Compounds of the present invention have also shown some affinity for the R2 isoform of MCHR. The compounds of the invention may also be used in combination with other approved therapeutic agents for the treatment and/or prevention of obesity and related diseases. In this format, the

compounds of the present invention ____________ the ositive effects of such approval combination treatments while minimizing the side effects due to the potential requirement of lower doses of such combination compounds. Such combination therapies may be delivered individually or in a combined formulation. Examples of compounds potentially useful in combination with compounds of formula I include weight loss agents (Mevidia™, Xenical™), cholesterol lowering agents, glucose level control or modulating agents and the like.

In treating non-human, non-companion animals, the compounds of the present invention are useful for reducing weight gain and/or improving the feed utilization efficiency and/or increasing lean body mass.

Formulation

The compound of formula I is preferably formulated in a unit dosage form prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of formula I and a pharmaceutical carrier.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a liquid, tablet, capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents,

sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Formulation Examples

Formulation 1

Tablets

Ingredient	Quantity (mg/tablet)
Active Ingredient	5 – 500
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Formulation 2

Suspensions

Ingredient	Quantity (mg/5 ml)
Active Ingredient	5 – 500 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve (approximately 355 micron opening) and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth

paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 3

Intravenous Solution

Ingredient	Quantity
Active Ingredient	25 mg
Isotonic saline	1,000 ml

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 ml per minute.

Dose

The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances, or by the vetrinarian for non-human recipients.

Generally, an effective minimum daily dose of a compound of formula I is about 5, 10, 15, or 20 mg. Typically, an effective maximum dose is about 500, 100, 60, 50, or 40 mg. Most typically, the dose ranges between 5 mg and 60 mg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the does until the desired therapeutic effect is observed.

Route of Administration

The compounds may be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes.

Combination Therapy

A compound of formula I may be used in combination with other drugs or therapies that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of formula I are useful. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of formula I. When a compound of formula I is used contemporaneously with one or more other drugs, a pharmaceutical unit dosage form containing such other drugs in addition to the compound of formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of formula I. Examples of other active ingredients that may be combined with a compound of formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) insulin sensitizers including (i) PPARγ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin;
(b) insulin or insulin mimetics;
(c) sulfonylureas such as tolbutamide and glipizide;
(d) alpha-glucosidase inhibitors (such as acarbose);
(e) cholesterol lowering agents such as
    i. HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins),
    ii. sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran),
    iii. nicotinyl alcohol nicotinic acid or a salt thereof,
    iv. proliferator-activator receptor a agonists such as fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate),

v. inhibitors of cholesterol absorption for example β-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide,

vi. probucol,

vii. vitamin E, and

viii. thyromimetics;

(f) PPARδ agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, and other β_3 adrenergic receptor agonists;

(h) feeding behavior modifying agents such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823;

(i) PPARα agonists such as described in WO 97/36579 by Glaxo;

(j) PPARγ antagonists as described in WO97/10813; and

(k) serotonin reuptake inhibitors such as fluoxetine and sertraline

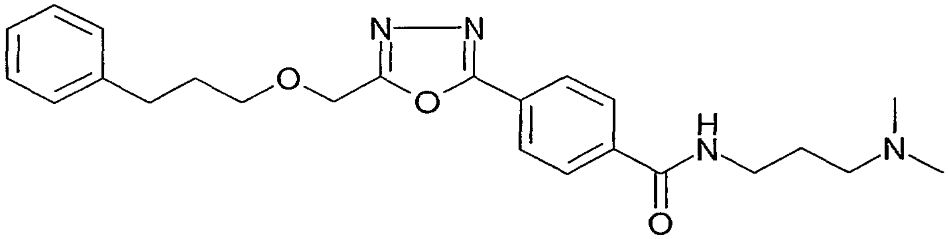
(l) antipsychotic agents such as for example olanzapine.

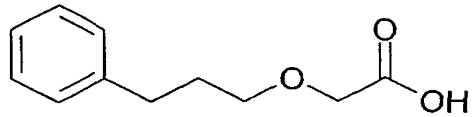
Examples

The following examples are only illustrative of the prepration protocols and Applicants' ability to prepare compounds of the present invention based on the schemes presented or modifications thereof. The examples are not intended to be exclusive or exhaustive of compounds made or obtainable .

Example 1

Preparation of *N*-(3-Dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 3-phenyl-1-propanol

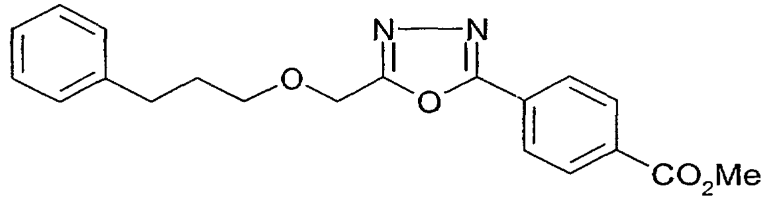


a) (3-Phenylpropoxy)acetic acid 

To a solution of 3-phenyl-1-propanol (5.0 g, 36.7 mmol) in 36 mL THF at room temperature was added, in portions, sodium hydride (1.54 g, 38.5 mmol). After 30 minutes, a solution of methyl bromoacetate (6.18 g, 40.4 mmol) in 18 mL THF was added and the resultant mixture stirred at room temperature for 4.1 hours. Next, the mixture was diluted with 20 mL H_2O, then lithium hydroxide (2.64 g, 110 mmol) was added and the biphasic solution was heated at 60°C for 1.5 hours. The mixture was then cooled to room temperature, diluted with Et_2O and washed three times with H_2O. The combined aqueous phases were acidified with concentrated HCl until pH < 2. The resultant mixture was extracted three times with Et_2O. The organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford an oil. Purification by flash filtration chromatography on silica gel (elution with CH_2Cl_2 followed by 9:1 CH_2Cl_2:MeOH) afforded 2.7 g (38%) of(3-phenylpropoxy)acetic acid as an oil.

^{1}H NMR (DMSO-d6) δ 7.30-7.15 (m, 5H), 3.99 (s, 2H), 3.5 (t, 2H, J=6 Hz), 2.63 (t, 2H, J=7 Hz), 1.76-1.85 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3027, 3019, 3013, 2948, 1779, 1732, 1454, 1246, and 1136.MS (ES) m/e 193. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found C, 68.58; H, 6.91

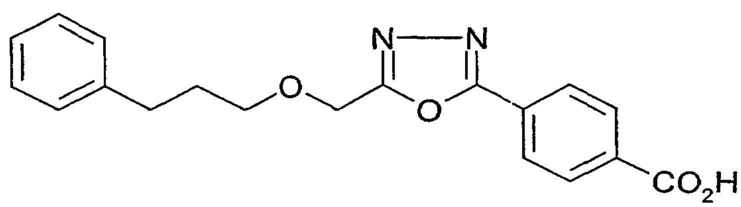
b) 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



To a solution of (3-phenylpropoxy)acetic acid (1.11 g, 5.7 mmol) in 14.6 mL toluene at room temperature was added 1,3-dicyclohexylcarbodiimide (1.11 g, 5.7 mmol). After five minutes, 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.16 g, 5.7 mmol) was added and the suspension was heated at 100°C for thirty minutes, then at 130°C for thirty minutes. The mixture was cooled to room temperature then diluted with CH_2Cl_2 and filtered. Concentration of the filtrate afforded a solid. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) followed by crystallization of the isolated material from Et_2O:hexane afforded 0.921 g (46%) of 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.17 (s, 4H), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.9 (s, 3H), 3.6 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=8 Hz), 1.8-1.9 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1722, 1438, 1283, 1111. MS (ES) m/e 353. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 67.78; H, 5.69; N, 7.74.

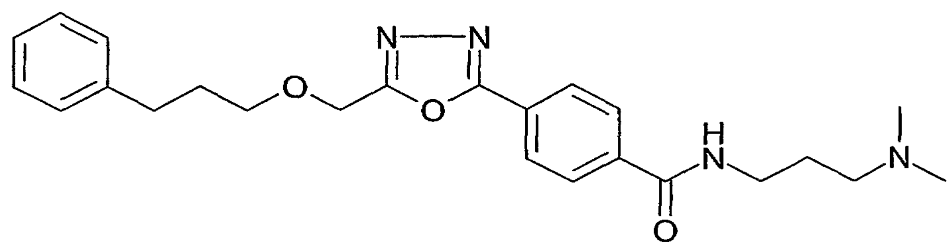
c) 4-[5-(3-Phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



A mixture of 4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.866 g, 2.5 mmol) and lithium hydroxide (0.177 g, 7.4 mmol) in 3.85 mL THF and 1.65 mL H_2O was stirred at 60°C for 1 hour. Upon cooling to room temperature the mixture was acidified with concentrated HCl (0.421 mL) and reduced in volume to remove the THF. The resulting insoluble material was collected by filtration to afford 0.760 g (91%) of 4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

^{1}H NMR (DMSO-d6) δ 8.1 (m, 4H), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.6 (t, 2H, J=6Hz) 2.6 (t, 2H, J=7Hz), 1.8-1.9 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3097, 3028, 2944, 2856, 2675, 2559, 1706, 1685, 1583, 1551, 1433, 1292, 1108, 874, 719. MS (ES) m/e 339, 337 Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 66.34; H, 5.31; N, 8.18.

d) *N*-(3-Dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide

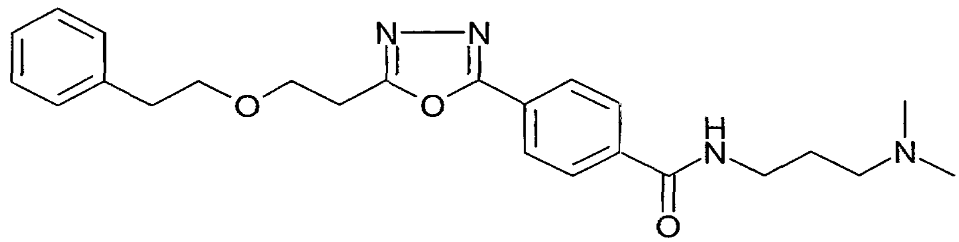


A mixture of 4-[5-(3-phenylpropoxymethyl)-[1,3,4] oxadiazol-2-yl]benzoic acid (0.730 g, 2.2 mmol) and 1,1'-carbonyldi-imidazole (0.367 g, 2.3 mmol) was stirred in 18 mL THF at 60°C for 45 minutes. After stirring an additional 45 minutes at room temperature, 3-(dimethylamino)propylamine (0.265 g, 2.59 mmol) was added. After stirring approximately 24 h at room temperature, the mixture was concentrated to an oil. The oil was treated with Et_2O and the resultant suspension was filtered. The filtrate was treated with hexane and the resultant crystals were collected by filtration to afford 0.451 g (49%) of *N*-(3-dimethylaminopropyl)-4-[5-(3-phenylpropoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

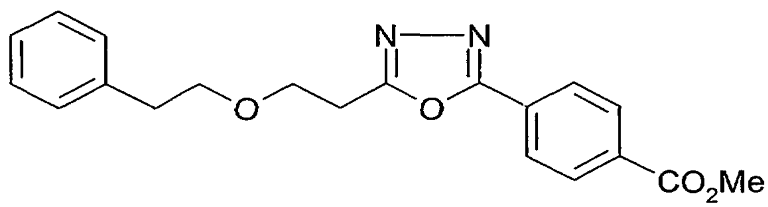
^{1}H NMR (DMSO-d6) δ 8.7 (d, 1H, J=5Hz), 8.1 (d, 2H, J=8Hz), 8.0 (d, 2H, J=8Hz), 7.1-7.3 (m, 5H), 4.8 (s, 2H), 3.5 (t, 2H, J=6Hz), 3.32 (m, 2H), 2.62 (t, 2H, J=7Hz), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.86 (m, 2H), 1.67 (m, 2H).

MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 67.89; H, 7.09; N, 13.15. Mp(°C)=90.

Example 2 N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide from 3-Phenethyloxypropionic acid



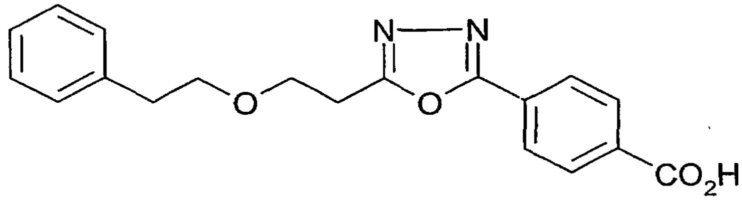
a) 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 3-Phenethyloxy propionic acid (1.02 g, 5.3 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.3 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.06 g, 5.2 mmol) to afford 0.79 g (43%) of 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid.

^{1}H NMR (DMSO-d6) δ 8.09-8.18 (m, 4H), 7.07-7.17 (m, 5H), 3.91 (s, 3H), 3.85 (t, 2H, J=6Hz), 3.65 (t, 2H, J=7Hz), 3.20 (t, 2H, J=6Hz), 2.78 (t, 2H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 3009, 2954, 2871, 1721, 1438, 1282, 1111. MS (ES) m/e, 353.Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 68.38; H, 5.66; N, 8.01.

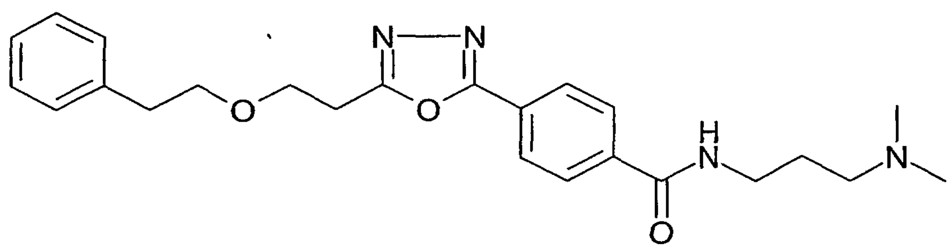
b) 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester 0.724 g, 2.1 mmol) and lithium hydroxide (0.148 g, 6.2 mmol) to afford 0.558 g (80%) of 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as solid.

^{1}H NMR (DMSO-d6) δ8.05-8.16 (m, 4H), 7.07-7.17 (m, 5H), 3.85 (t, 2H, J=6Hz), 3.65 (t, 2H, J=7Hz), 3.20 (t, 2H, J=6Hz), 2.78 (t, 2H, J=7Hz). IR (KBr, cm^{-1}) 3431, 1705, 1685, 1434, 1290, 1118, 715. MS (ES) m/e, 339, 337.Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 64.37; H, 5.08; N, 9.05.

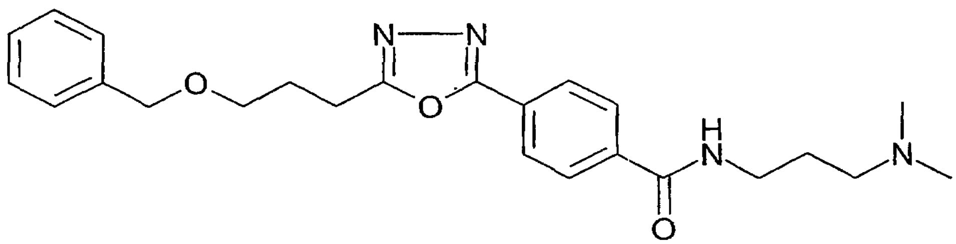
c) N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide



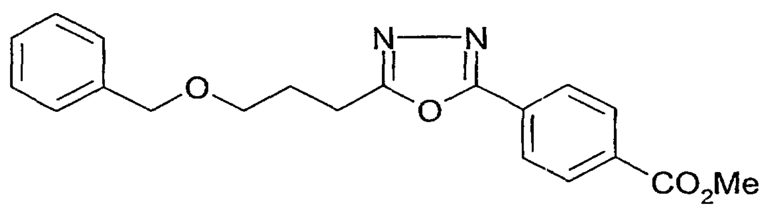
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-Phenethyloxyethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.528 g, 1.6 mmol), 1,1'-carbonyldiimidazole (0.266 g, 1.6 mmol) and 3-(dimethylamino)propylamine (0.392 g, 3.8 mmol) to afford 0.309g (47%) of N-(3-Dimethylaminopropyl)-4-[5-(2-phenethyloxyethyl)-[1,3,4-oxadiazol-2-yl]benzamide as a crystalline solid.

^{1}H NMR (DMSO-d6) δ8.71 (t, 1H, J=5Hz), 8.05 (d, 2H, J=9Hz), 8.02 (d, 2H, J=9Hz), 7.09-7.17 (m, 5H), 3.85 (t, 2H,J=9Hz), 3.65 (t, 2H, J=7Hz), 3.29 (m, 2H), 3.19 (t, 2H, J=6Hz), 2.78 (t, 2H, J=7Hz), 2.26 (t, 2H,J=7Hz), 2.14 (s, 6H), 1.66 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3307, 2942, 2879, 2761, 1631, 1540, 1116, 858, 699. MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 67.83; H, 7.24; N, 13.19. Mp(°C)=92.

Example 3 Preparation of 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzamide from 4-benzyloxybutyric acid



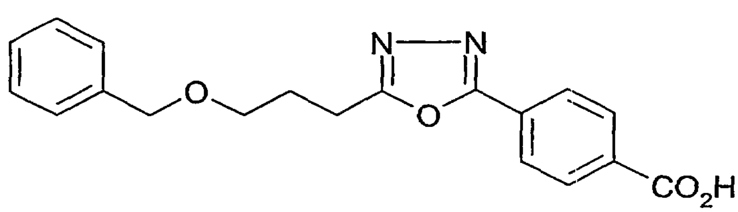
a) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-benzyloxybutyric acid (0.725 g, 3.7 mmol), 1,3-dicyclohexylcarbodiimide (0.771 g, 3.7 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.755 g, 3.7 mmol) to afford 0.733 g (56%) of 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid methyl ester as a crystalline solid.

^{1}H NMR (DMSO-d6) δ8.09-8.16 (m, 4H), 7.23-7.30 (m, 5H), 4.46 (s, 2H), 3.90 (s, 3H), 3.56 (t, 2H, J=6Hz), 3.03 (t, 2H, J=7Hz), 2.07 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1721, 1438, 1282, 1111. MS (ES) m/e, 353. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 68.10; H, 5.79; N, 8.03.

b) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid

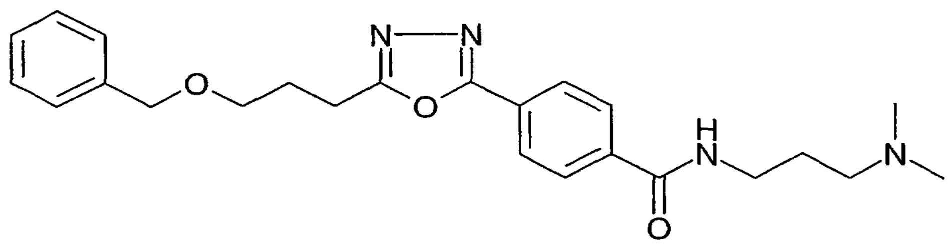


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzoic acid methyl ester (0.669 g, 1.9 mmol) and lithium

hydroxide (0.136 g, 5.7 mmol) to afford 0.610 g (95%) 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzoic acid as a solid.

^{1}H NMR (DMSO-d6) δ 8.06-8.14 (m, 4H), 7.23-7.29 (m, 5H), 4.46 (s, 2H), 3.56 (t, 2H, J=6Hz), 3.03 (t, 2H, J=7Hz), 2.02-2.11 (m, 2H). IR (KBr, cm^{-1}) 2859, 1681, 1428, 1321, 1292, 1119, 720. MS (ES) m/e, 339, 337. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 67.15; H, 5.36; N, 8.32.

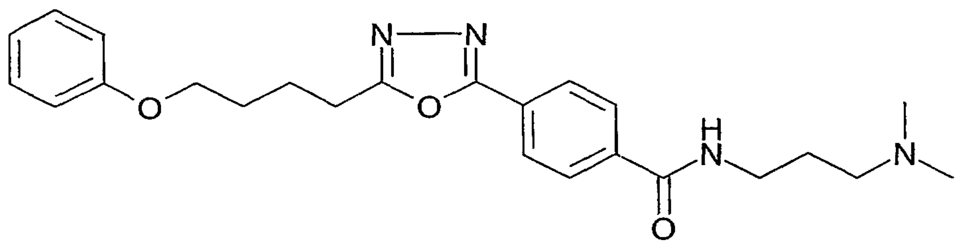
c) 4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethylaminopropyl)benzamide



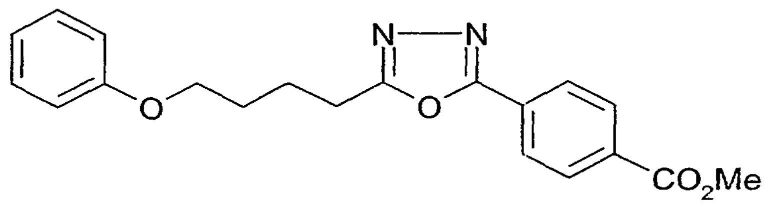
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from (4-[5-(3-Benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzoic acid (0.580 g, 1.7 mmol), 1,1'-carbonyl diimidazole (0.291 g, 1.8 mmol) and 3-(dimethylamino)propyl amine (0.210 g, 2.1 mmol) to afford 0.408 g (56%) 4-[5-(3-benzyloxypropyl)-[1,3,4]oxadiazol-2-yl]-N-(3-dimethyl aminopropyl)benzamide as a crystalline material.

^{1}H NMR (DMSO-d6) δ8.69 (m, 1H), 7.99-8.07 (m, 4H), 7.28 (m, 5H), 4.46 (s, 2H), 3.55 (t, 2H, J=6Hz), 3.30 (m, 2H), 3.02 (t, 2H, J=7Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 2.06 (m, 2H), 1.66 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3008, 2864, 2827, 1651, 1587, 1556, 1494, 1093. MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 67.24; H, 6.01; N, 12.84. Analytical HPLC: 100% purity. Mp(°C)= 106

Example 4 Preparation of N-(3-Dimethylaminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide from 5-phenoxypentanoic acid



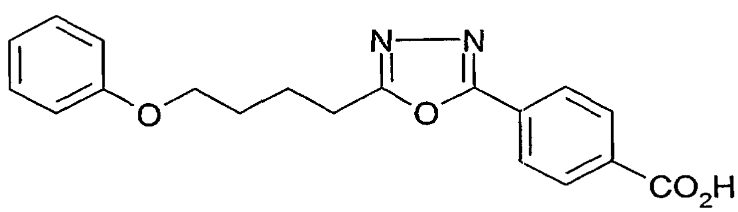
a) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 5-phenoxypentanoic acid (1.02 g, 5.3 mmol), 1,3-dicyclohexylcarbodiimide (1.08 g, 5.3 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.06 g, 5.2 mmol) to afford 0.639 g (38%) of 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline material.

^{1}H NMR (DMSO-d6) δ 8.10 (m, 4H), 7.23-7.29 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.90 (s, 3H), 3.04 (t, 2H, J=7Hz), 1.83-1.98 (m, 4H).IR ($CHCl_3$, cm^{-1}) 1721, 1587, 1498, 1438, 1283, 1245, 1111. MS (ES) m/e, 353. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found C, 67.89; H, 5.58; N, 7.91.

b) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

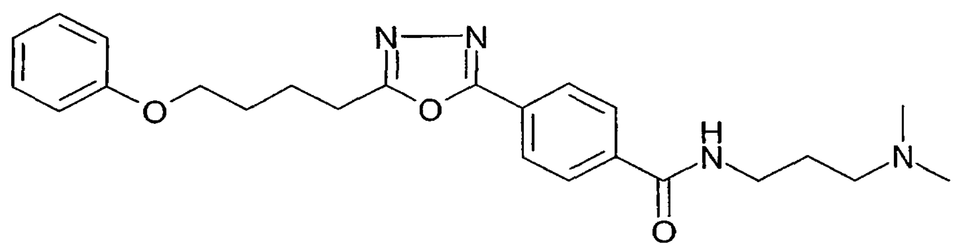


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.560 g, 1.6 mmol) and lithium hydroxide (0.114 g, 4.8 mmol) to afford 0.491 g (91%) of 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a solid.

^{1}H NMR (DMSO-d6) δ 8.08-8.15 (m, 4H), 7.23-7.30 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.04 (t, 2H, J=7Hz), 1.81-2.00 (m, 4H). IR (KBr, cm^{-1}) 1684, 1585,

1501, 1321, 1292, 1256, 723. MS (ES) m/e, 339, 337. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found C, 66.79; H, 5.40; N, 8.27.

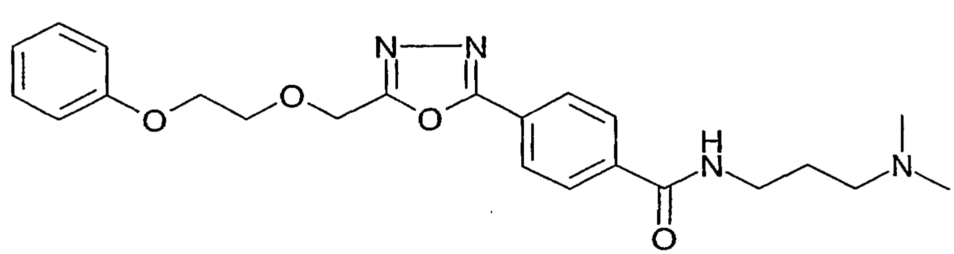
c) N-(3-Dimethylaminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide



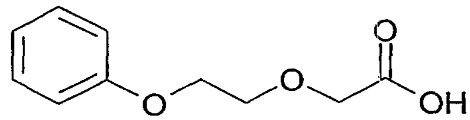
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.461 g, 1.4 mmol), 1,1'-carbonyldiimidazole (0.231 g, 1.4 mmol) and 3-(dimethylamino)propylamine (0.167 g, 1.6 mmol) to afford the title compound as a crude mixture. Crystallization of the material from EtOAc afforded 0.237 g (40%) of N-(3-dimethyl-aminopropyl)4-[5-(4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]benzamide.

^{1}H NMR (DMSO-d6) δ 8.70 (m, 1H), 8.00-8.08 (m, 4H), 7.23-7.30 (m, 2H), 6.88-6.94 (m, 3H), 4.02 (t, 2H, J=6Hz), 3.32 (m, 2H), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.83-1.98 (m, 4H), 1.62-1.72 (m, 2H). IR (KBr, cm^{-1}) 3310, 2953, 2763, 1634, 1563, 1540, 1498, 1253, 1249, 1010, 855, 749. MS (ES) m/e, 423, 421. Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found C, 68.25; H, 7.21; N, 12.82. Analytical HPLC: 100% purity. Mp(°C)=114.

Example 5 Preparation of N-(Dimethylaminopropyl)4-[5-(2-phenoxy-ethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 2-phenoxyethanol



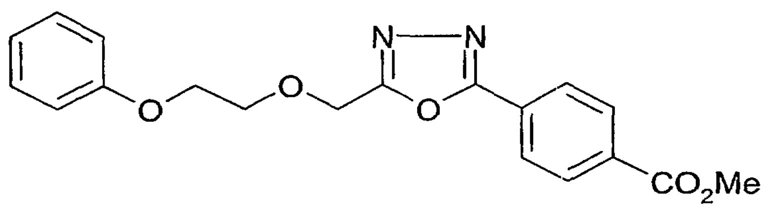
a) 2-(Phenoxyethoxy)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1a, from 2-phenoxyethanol (5.4 g, 38.9 mmol) and methyl bromoacetate (6.55 g, 42.8 mmol), then, using lithium hydroxide (2.78 g 116.1 mmol) to afford 5.9 g (77%) of 2-(phenoxyethoxy)acetic acid as an oil.

^{1}H NMR (DMSO-d6) δ 7.25-7.31 (m, 2H), 6.93 (m, 3H), 4.11 (m, 4H), 3.81 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1733, 1600, 1589, 1498, 1245, 1144. MS (ES) m/e, 197, 195. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found C, 61.49; H, 5.70.

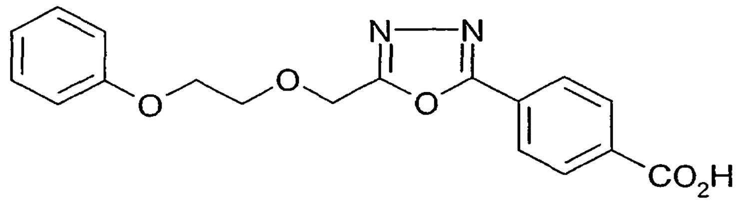
b) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 2-(phenoxyethoxy)acetic acid (1.08 g, 5.5 mmol), 1,3-dicyclohexylcarbodiimide (0.957 g, 4.6 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.938 g, 4.6 mmol) to afford 0.559 g (35%) of 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid contaminated with 1,3-dicyclohexylurea.

^{1}H NMR (DMSO-d6) δ 8.15 (m, 4H), 7.22-7.29 (m, 2H), 6.89-6.94 (m, 3H), 4.92 (s, 2H), 4.15 (m, 2H), 3.92-4.17 (m, 2H), 3.91 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3328, 2850, 1719, 1601, 1565, 1441, 1296, 1282, 1254, 1146, 1137, 1112, 759, 715. MS (ES) m/e, 355. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found C, 64.72; H, 5.66; N, 8.37.

c) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid

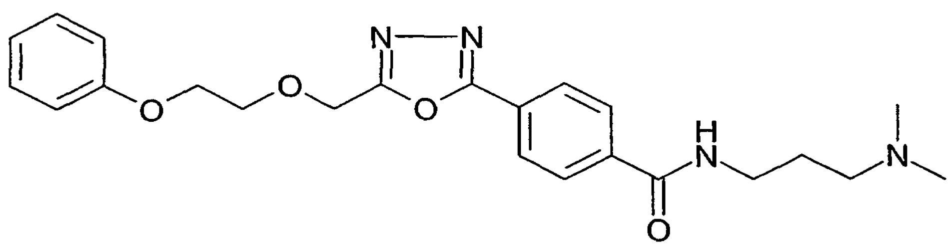


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.500 g, 1.4 mmol) and lithium hydroxide (0.101 g, 4.2 mmol) to afford 0.366 g (76%) as a solid contaminated with 1,3-dicyclohexylurea.

^{1}H NMR (DMSO-d6) δ 7.95-8.06 (m, 4H), 7.26-7.32 (m, 2H), 6.91-6.98 (m, 3H), 4.14-4.19 (m, 4H), 3.88 (m, 2H).

IR (KBr, cm^{-1})3327, 2928, 2850, 1700, 1685, 1625, 1608, 1246, 1132, 691. MS (ES) m/e, 339. Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.53; H, 4.74; N, 8.23. Found C, 61.01; H, 5.65; N, 8.32.

d) N-(Dimethylaminopropyl)4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide

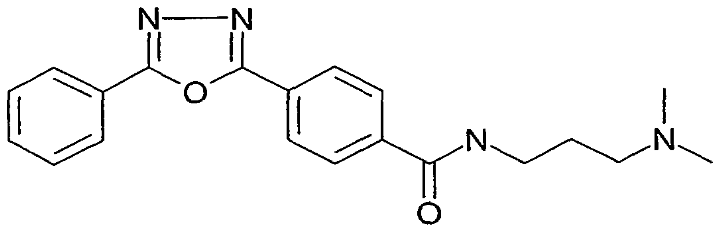


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid 0.333 g, 0.98 mmol), 1,1'-carbonyldiimidazole (0.160 g, 0.99 mmol) and 3-(dimethylamino)propylamine (0.099 g, 1.0 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eluted with 10% 2M NH_3 in MeOH:$CHCl_3$) afforded 0.03 g (7%) of N-(dimethylamino propyl)4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]benzamide as a solid.

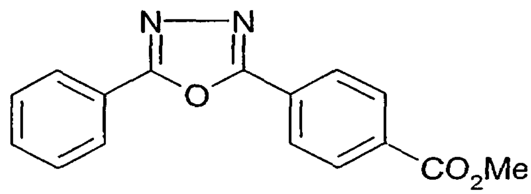
^{1}H NMR (DMSO-d6) δ 8.72 (t, 1H, J=5Hz), 8.01-8.10 (m, 4H), 7.23-7.29 (m, 2H), 6.89-6.96 (m, 3H), 4.19 (s, 2H), 4.15 (m, 2H), 3.93 (m, 2H), 3.31 (m, 2H), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.72 (m, 2H).IR ($CHCl_3$, cm^{-1}) 4446, 2936, 2763, 1637,

1530, 1490, 1253, 1047, 752. MS (ES) m/e, 425, 423. Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65; N, 13.20. Found C, 64.74; H, 6.58; N, 12.98. Mp(°C)=146.

Example 6 Preparation of N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide from benzoyl chloride.



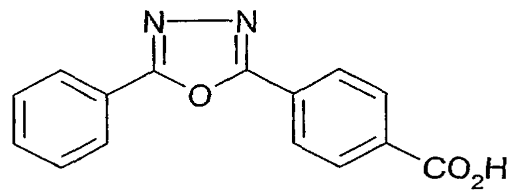
a) 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



A suspension of 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.00 g, 4.9 mmol) and pyridine (0.391 g, 5.0 mmol) in 7.3 mL toluene stirring at room temperature was added benzoyl chloride. The resultant heavy white suspension was heated at 100 °C for twenty minutes then at 140 °C for twenty minutes. After cooling to room temperature the mixture was treated with EtOAc and H_2O. The suspension was triterated then filtered to afford 0.652 g (48%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester. The filtrate phases were separated. The organic phase was dried over sodium sulfate, filtered, concentrated to afford a solid. The solid was crystallized from acetone: diethyl ether to afford 0.371 (27%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^1H NMR (DMSO-d6) δ 8.27 (m, 2H), 8.16 (m, 4H), 7.62-7.71 (m, 3H), 3.91 (s, 3H). IR (KBr, cm^{-1}) 1723, 1545,1447, 1442, 1280, 1118,1110,1018, 780, 717, 688. MS (ES) m/e, 281. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found C, 68.47; H, 4.42; N, 10.03.

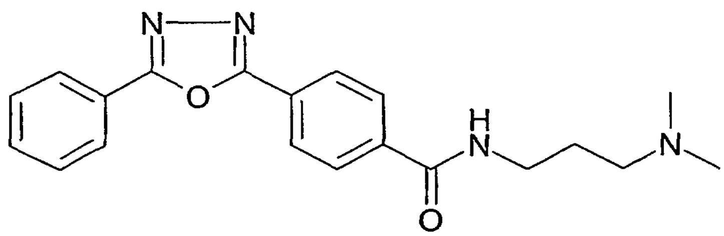
b) 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.938 g, 3.3 mmol) and lithium hydroxide (0.240 g, 10.0 mmol) to afford 0.889 g (100%) of 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid as a solid.

^{1}H NMR (DMSO-d6) δ13.29 (bs, 1H), 8.21-8.28 (m, 2H), 8.13-8.19 (m, 4H), 7.61-7.69 (m, 3H). IR (KBr, cm^{-1}) 3436, 1683, 1547, 1425, 1287, 718, 689. MS (ES) m/e, 267, 265. Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found C, 64.26; H, 3.76; N, 9.94.

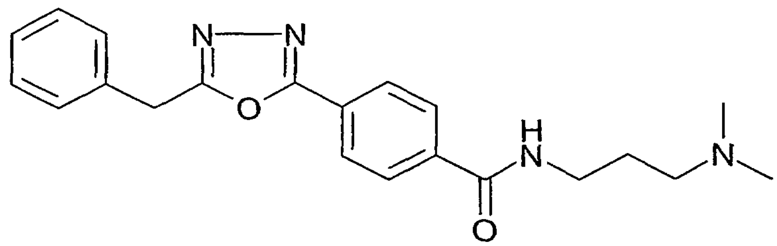
c) N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide



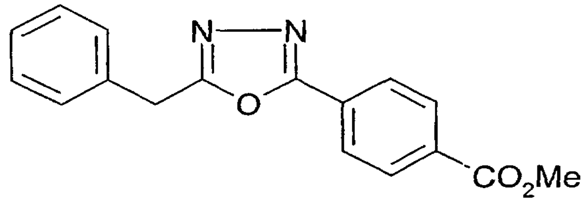
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.536 g, 2.0 mmol), 1,1'-carbonyldiimidazole (0.3300 g, 2.0 mmol) and 3-(dimethylamino)propylamine (0.412 g, 4.0 mmol) and 1.3 mL DMF to afford a solid. Crystallization from methanol:diethyl ether afforded 0.286 g (41%) of N-(3-Dimethylaminopropyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)benzamide.

^{1}H NMR (DMSO-d6) δ 8.73 (t, 1H, J=5Hz), 8.23 (d, 2H, J=7Hz), 8.15-8.20 (m, 2H), 8.05 (d, 2H, J=7Hz), 7.61-7.69 (m, 3H), 3.31 (m, 2H), 2.27 (t, 2H, J=7Hz), 3.31 (m, 2H), 1.63-1.73 (m, 2H). IR (KBr, cm^{-1}) 3330, 2941, 2763, 1667, 1646, 1547, 1492, 715. MS (ES) m/e,351, 349. Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found C, 68.08; H, 6.29; N, 15.90. Mp(°C)=130.

Example 7 Preparation of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide from phenylacetic acid.



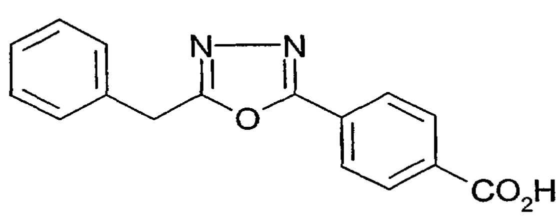
a) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from phenyl acetic acid (0.470 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.5 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.421 g (69%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.08-8.16 (m, 4H), 7.28-7.41 (m, 5H), 4.39 9s, 2H), 3.89 (s, 3H). IR (KBr, cm^{-1}) 1716, 1559, 1551, 1435, 1276, 1111, 779, 728, 723, 710. MS (ES) m/e, 295. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found C, 69.27; H, 4.78; N, 9.52.

b) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid

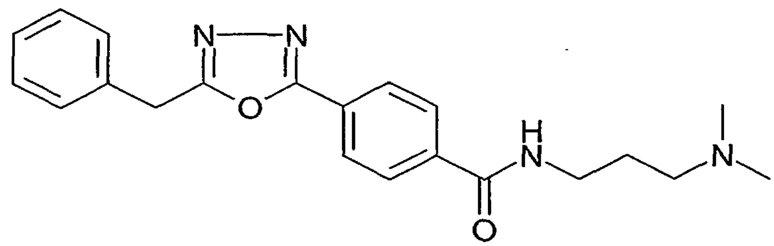


A mixture of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.413 g, 1.4 mmol) and lithium hydroxide (0.125 g, 5.2 mmol) in 4.1 mL THF and 1.8 mL H_2O

was stirred at room temperature for fours hours. Next, concentrated HCl (450 uL, 5.2 mmol) was added. The resultant suspension was reduced in volume then filtered to afford 0.393 g (85%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.33 (bs, 1H), 8.06-8.14 (m, 4H), 7.27-7.42 (m, 5H), 4.39 (s, 2H). IR (KBr, cm^{-1}) 1706, 1685, 1583, 1563, 1552, 1432, 1323, 1290, 872, 716, 706. MS (ES) m/e, 281, 279. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found C, 68.38; H, 4.43; N, 9.99.

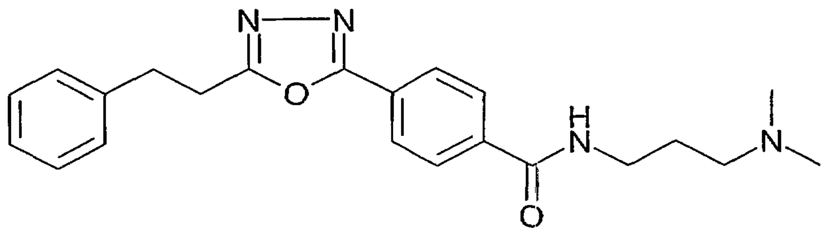
c) 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide



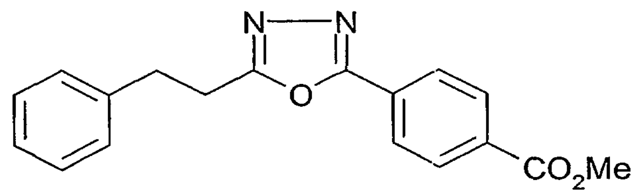
A suspension of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.255 g, 0.91 mmol), 1-hydroxybenzotriazole (0.123 g, 0.91 mmol), 4-dimethylamino pyridine (0.011 g, 0.09 mmol) and 1,3-dicyclohexylcarbodiimide (0.206 g, 1.00 mmol) in 26 mL CH_2Cl_2 was stirred at room temperature for fifteen minutes. Next, 3-(dimethylamino)propyl amine (0.093 g, 0.91 mmol) was added and the reaction was stirred 21 hours at room temperature. The suspension was filtered and the filtrate was reduced in volume. Purification by radial chromatography on silica gel (elution with 90:10:1 CH_2Cl_2:MeOH:NH_4OH) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.054 g (16%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylaminopropyl)benzamide. A second lot of crystals was obtained to afford 0.017 g (5%) of 4-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)benzamide.

^{1}H NMR (DMSO-d6) δ8.70 (t, 1H, J=5Hz), 8.04 (d, 2H, J=9Hz), 8.00 (d, 2H, J=9Hz), 7.29-7.41 (m, 5H), 4.38 (s, 2H), 3.31 (m, 2H), 2.25 (t, 2H, J=7Hz), 2.13 (s, 6H), 1.61-1.70 (m, 2H). IR (KBr, cm^{-1}) 3298, 2943, 2768, 1937,1636, 1555, 1324, 1087, 863, 721, 706. MS (ES) m/e, 365, 363. Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found C, 68.91; H, 6.71; N, 15.38. Mp(°C)=110.

Example 8 Preparation of N-(3-dimethylaminopropyl)-4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzamide from hydrocinnamoyl chloride



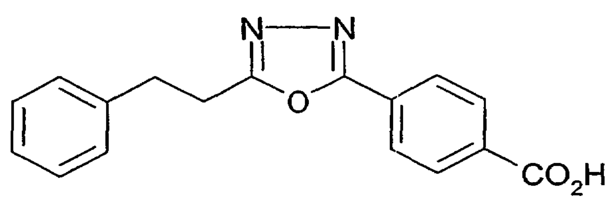
a) 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



A solution of 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.00 g, 4.9 mmol) and hydrocinnamoyl chloride (0.826 g, 4.9 mmol) in 10 mL toluene was heated at 100 $^{\square}$C for five hours. The mixture was then concentrated to an oil. The oil was dissolved into CH_2Cl_2 and washed with 0.1 N HCl. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over sodium sulfate, filtered and concentrated to afford a solid. Purification by HPLC on silica gel (eluted with a linear gradient of 10 to 25% EtOAc:toluene over a thirty minute period) afforded 0.604 g (40%) of4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester as a white solid.

^{1}H NMR (DMSO-d6) δ 8.15 (d, 2H, J=9Hz), 8.09 (d, 2H, J=9Hz), 7.18-7.31 (m, 5H), 3.90 (s, 3H), 3.28 (t, 2H, J=7Hz), 3.12 (t, 2H, J=7Hz). IR (KBr, cm^{-1}) 1714, 1415, 1278, 1111, 774, 713, 696. MS (ES) m/e, 309. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found C, 69.55; H, 5.14; N, 9.03.

b) 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid

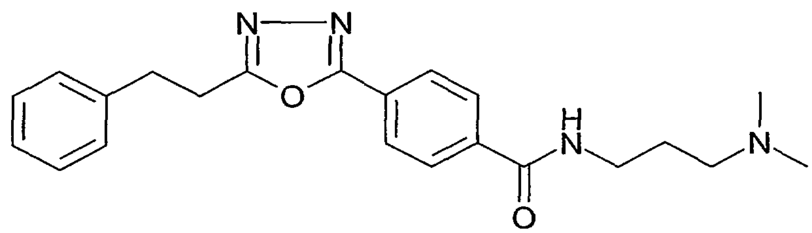


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid

methyl ester (0.600 g, 2.0 mmol) and lithium hydroxide (0.140 g, 5.8 mmol), to afford 0.510 g (89%) of 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.33 (bs, 1H), 8.13 (d, 2H, J=9Hz), 8.07 (d, 2H, J=9Hz), 7.18-7.33 (m, 5H), 3.28 (t, 2H, J=7Hz), 3.12 (t, 2H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 1670, 1568, 1555, 1420, 1280, 1017. MS (ES) m/e, 295, 293. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found C, 68.95; H, 4.57; N, 9.40.

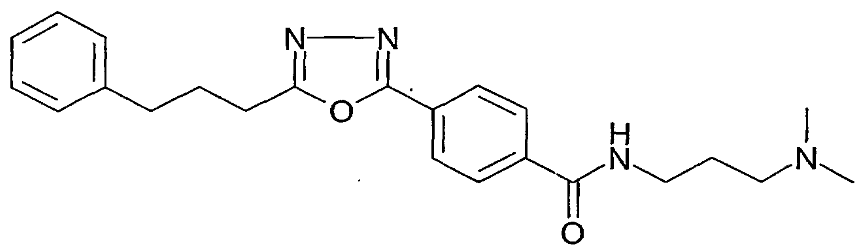
c) N-(3-dimethylaminopropyl)-4-(5—phenethyl-[1,3,4] oxadiazol-2-yl)benzamide



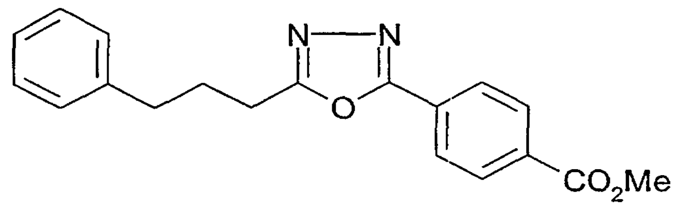
A suspension of 4-(5—phenethyl-[1,3,4]oxadiazol-2-yl)benzoic acid (0.480 g, 1.6 mmol), 1-hydroxybenzotriazole (0.337 g, 2.5 mmol), 3-(dimethylamino)propyl amine (0.286 g, 2.8 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.597 g, 3.11 mmol) in 46 mL THF was stirred at room temperature for twenty four hours. The resultant suspension was filtered and the filtrate was concentrated to an oil. The oil was dissolved into EtOAc then washed with 2N sodium hydroxide (2 x 25 ml), water then brine. The organic phase was dried over sodium sulfate, filtered, concentrated to afford a white solid. Crystallization of this material from methanol:diethyl ether affored 0.354 g (57%) of N-(3-dimethylaminopropyl)-4-(5—phenethyl)-[1,3,4]oxadiazol-2-yl)benzamide.

^{1}H NMR (DMSO-d6) δ 8.70 (t, 1H, J=5Hz), 8.04 (d, 2H, J=9Hz), 8.01 (d, 2H, J=9Hz), 7.19-7.30 (m, 5H), 3.26-3.33 (m, 4H), 3.12 (t, 2H, J=8Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.71 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3346, 2973, 2942, 2813, 2764, 1636, 1585, 1564, 1552, 1530, 1496, 1496, 1287. MS (ES) m/e,379, 377. Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80. Found C, 69.62; H, 6.84; N, 14.80. Mp(°C)=126.

Example 9 Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzamide from 4-phenylbutyric acid



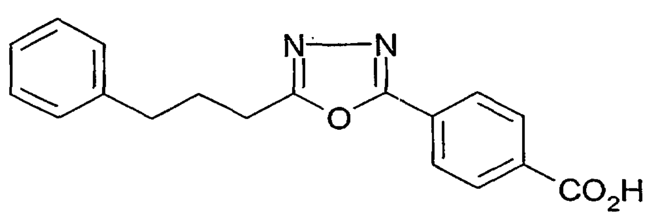
a) 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-phenylbutyric acid (0.470 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.4 mmol) and 5.1 mL toluene to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.554 g (50%) of 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.14 (d, 2H, J=6Hz), 8.11 (d, 2H, J=6Hz), 7.15-7.32 (m, 5H), 3.90 (s, 3H), 2.95 (t, 2H, J=7Hz), 2.72 (t, 2H, J=7Hz), 2.04-2.14 (m, 2H). IR (KBr, cm^{-1}) 1724, 1713, 1587, 1572, 1415, 1281, 1275, 1114, 1107,751, 718. MS (ES) m/e, 323. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 70.60; H, 5.65; N, 8.71.

b) 4-[5—(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzoic acid

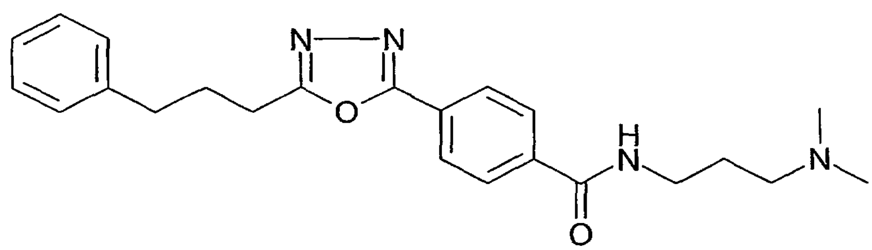


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzoic

acid methyl ester (0.512 g, 1.6 mmol) and lithium hydroxide (0.092 g, 3.8 mmol) to afford 0.333 g (85%) of 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ13.33 (bs, 1H), 8.12 (d, 2H, J=9Hz), 8.08 (d, 2H, J=9Hz), 7.15-7.32 (m, 5H), 2.95 (t, 2H, J=7Hz), 2.72 (t, 2H, J=7Hz), 2.04-2.14 (m, 2H). IR (KBr, cm^{-1}) 1685, 1565, 1322, 1302, 1287, 722. MS (ES) m/e, 309, 307. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found C, 70.05; H, 5.20; N, 9.00.

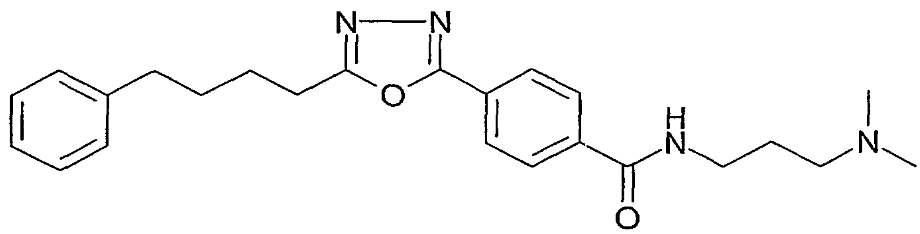
c) N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzamide



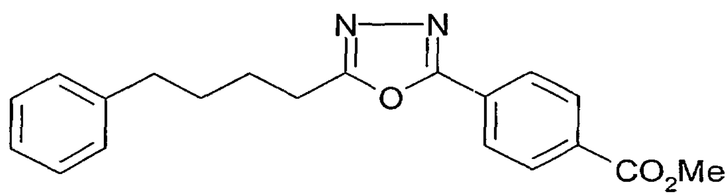
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzoic acid (0.430 g, 1.39 mmol), 1-hydroxybenzotriazole (0.188 g, 1.39 mmol), 4-dimethylamino pyridine 0.150 g, 1.46 mmol), 3-(dimethylamino)propylamine (0.150 g, 1.46 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eltuted with 10% 2M ammonium:CH_2Cl_2) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.274 g (50%) of N-(3-dimethylaminopropyl)-4-(5-phenylpropyl)-[1,3,4]oxadiazol-2-yl)benzamide.

^{1}H NMR (DMSO-d6) δ 8.70 (t, 1H, J=5Hz), 7.99-8.08 (m, 4H), 7.16-7.33 (m, 5H), 3.53 (m, 2H), 3.30 (t, 2H, J=7Hz), 2.72 (t, 2H, J=7Hz), 2.27 (t, 2H, J=7Hz), 2.13 (s, 6H), 2.04-2.11 (m, 2H), 1.63-1.72 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3008, 2950, 2827, 1652, 1586, 1567, 1557, 1529, 1495, 1243, 1089. MS (ES) m/e,393, 391.Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 70.38; H, 7.19; N, 14.27. Found C, 69.78; H, 7.04; N, 14.04. Analytical HPLC: 100% purity. Mp(°C)>200.

Example 10Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzamide from 5-phenylvaleric acid



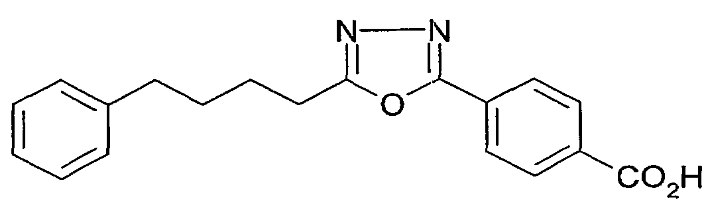
a) 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 5-phenylvaleric acid (0.620 g, 3.5 mmol), 1,3-dicyclohexylcarbodiimide (0.710 g, 3.5 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.4 mmol) and 5.1 mL toluene to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc : hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.463 g (40%) of 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.09-8.17 (m, 4H), 7.14-7.30 (m, 5H), 3.90 (s, 3H), 2.99 (t, 2H, J=7Hz), 2.64 (t, 2H, J=7Hz), 1.65-1.85 (m, 4H). IR (KBr, cm^{-1}) 1723, 1568, 1413, 1277, 1111, 716, 697. MS (ES) m/e, 337. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found C, 71.36; H, 5.90; N, 8.29.

b) 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzoic acid

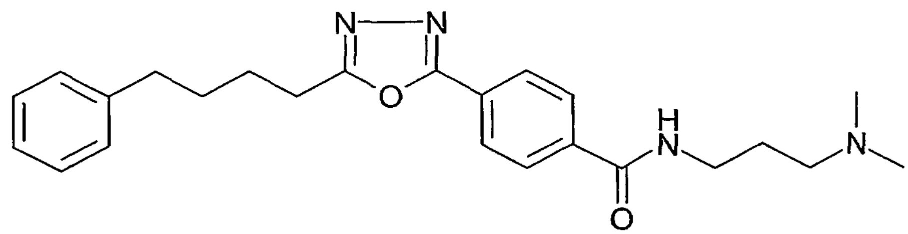


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, using 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzoic acid

methyl ester (0.380 g, 1.16 mmol) and lithium hydroxide (0.081 g, 3.4 mmol) to afford 0.360 g (99%) of 4-[5-(3-phenylbutyl)-[1,3,4]oxa-diazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.38 (bs, 1H),8.04-8.14 (m, 4H), 7.14-7.30 (m, 5H), 2.99 (t, 2H, J=7Hz), 2.64 (t, 2H, J=7Hz), 1.64-1.85 (m, 4H). IR (KBr, cm^{-1}) 2946,1686, 1586, 1567, 1551, 1429, 1413, 1320, 1288, 740, 716. MS (ES) m/e, 323, 321. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 70.33; H, 5.38; N, 8.41.

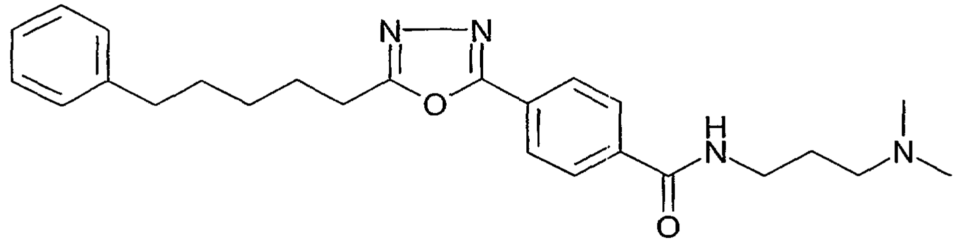
c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzamide



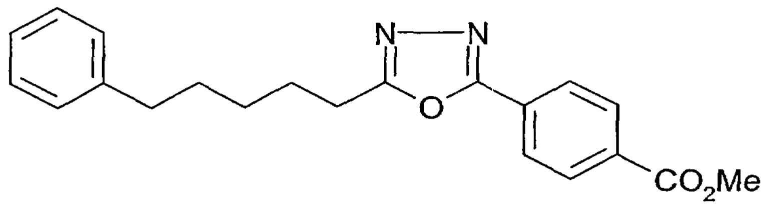
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzoic acid (0.342 g, 1.0 mmol), 1-hydroxybenzotriazole 0.136 g, 1.0 mmol), 4-dimethylamino pyridine (0.012 g, 0.10 mmol), 3-(dimethylamino)propylamine (0.108 g, 1.06 mmol) and 29 mL CH_2Cl_2. Purification by radial chromatography on silica gel (eluted with 10% 2M ammonium:CH_2Cl_2) followed by crystallization of the iosolated material from ethanol:diethyl ether afforded 0.226 g (55%) of 4[5-(3-dimethylaminopropyl)-4-(5—phenylbutyl)-[1,3,4]oxadiazol-2-yl)benzamide.

^{1}H NMR (DMSO-d6) δ 8.71 (t, 1H, J=5Hz), 7.99-8.06 (m, 4H), 7.14-7.30 (m, 5H), 3.32 (m, 2H), 2.98 (t, 2H, J=7Hz), 2.64 (t, 2H, J=7Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.82 (m, 6H). IR ($CHCl_3$, cm^{-1}) 3008, 2947, 1652, 1586, 1567, 1556, 1529, 1495. MS (ES) m/e, 407, 405. Anal. Calcd for $C_{24}H_{30}N_4O_2$: C, 70.91; H, 7.44; N, 13.78. Found C, 70.66; H, 7.35; N, 13.67. Mp(°C)=84.

Example 11Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzamide from 6-phenylhexanoic acid



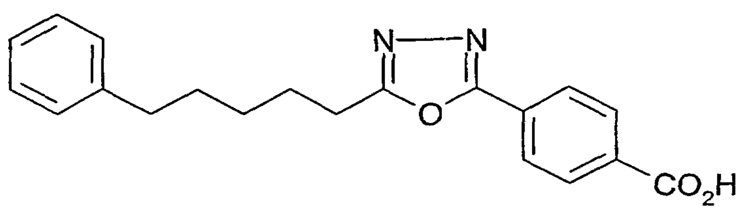
a) 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 6-phenylhexanoic acid (0.960 g, 5.0 mmol), 1,3-dicyclohexylcarbodiimide (1.01 g, 5.0 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.01 g, 4.95 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc : hexane) afforded 0.766 g (44%) of 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.10-8.17 (m, 4H), 7.11-7.28 (m, 5H), 3.90 (s, 3H), 2.95(t, 2H, J=7Hz), 2.59 (t, 2H, J=8Hz), 1.81 (dt, 2H, J=8Hz), 1.63 (dt, 2H, J=8Hz), 1.35-1.45 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3010, 2938, 2860, 1721, 1569, 1438, 1282, 1119, 1111. MS (ES) m/e, 351. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found C, 72.04; H, 6.32; N, 8.00.

b) 4-[5—(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic acid

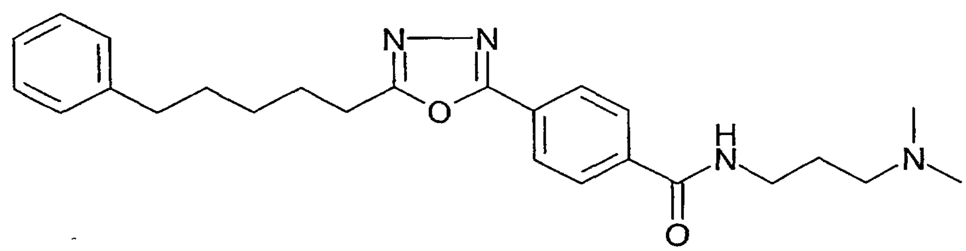


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic

acid methyl ester (0.7.25 g, 2.1 mmol), lithium hydroxide (0.149 g, 6.2 mmol) to afford 0.685 g (98%) of 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.33 (bs, 1H), 8.07-8.15 (m, 4H), 7.12-7.28 (m, 5H), 2.95 (t, 2H, J=7Hz), 2.59 (t, 2H, J=7Hz), 1.74-1.86 (m, 2H), 1.56-1.70 (m, 2H), 1.35-1.45 (m, 2H). IR (KBr, cm^{-1}) 2949, 2919, 2856, 1683, 1570, 1321, 1291, 732, 720. MS (ES) m/e, 337, 335. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found C, 70.86; H, 5.96; N, 8.26.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzamide

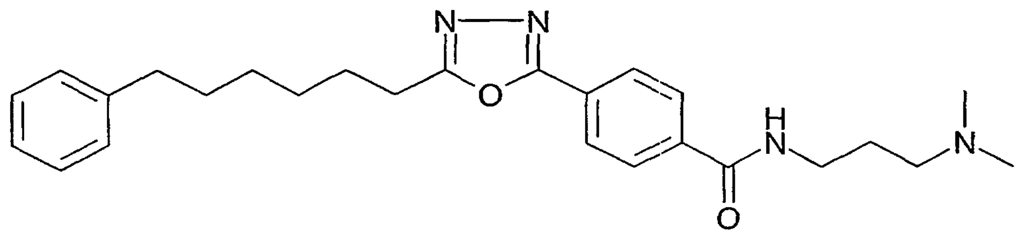


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzoic acid (0.500 g, 1.49 mmol), 1-hydroxybenzotriazole (0.201 g, 1.49 mmol), 4-dimethylamino pyridine (0.018 g, 0.15 mmol), and 3-(dimethylamino)propylamine (0.159 g, 1.56 mmol) to afford the title compound as a crude mixture. Purification by chromatography on silica gel (eltuted with a linear gradient of 2 to 10% 2M ammonium:CH_2Cl_2 over a thirty minute period) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.209 g (33%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzamide. A second crop of crystals afforded 0.085g (13%) of the title compound.

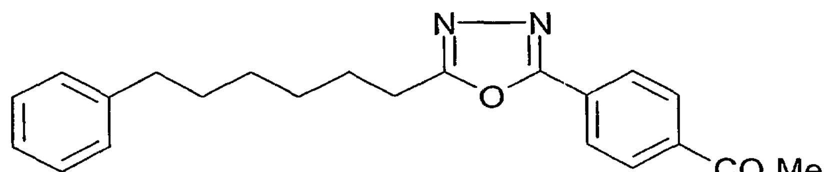
^{1}H NMR (DMSO-d6) δ 8.71 (t, 1H, J=5Hz), 8.00-8.07 (m, 4H), 7.12-7.28 (m, 5H), 3.30 (m, 2H), 2.94 (t, 2H, J=7Hz), 2.59 (t, 2H, J=7Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.76-1.86 (m, 2H), 1.58-1.71 (m, 4H), 1.37-1.45 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3007, 1652, 1586, 1555, 1529, 1494. MS (ES) m/e, 421, 419. Anal. Calcd for $C_{25}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found C, 71.16; H, 7.64; N, 13.23. Mp(°C)=116.

Example 12

Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl)benzamide from 7-phenylheptanoic acid



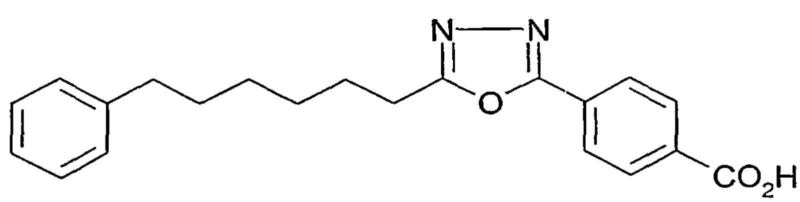
a) 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 7-phenylheptanoic acid (0.714 g, 3.46 mmol), 1,3-dicyclohexylcarbodiimide (0.714 g, 3.46 mmol), 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.43 mmol) and 5.1 mL toluene to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc:hexane) afforded 0.738 g (59%) of 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.10-8.17 (m, 4H), 7.12-7.28 (m,5H), 3.90 (s, 3H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.72-1.82 (m, 2H), 1.53-1.63 (m, 2H), 1.28-1.46 (m, 4H). IR (KBr, cm^{-1}) 2952, 2930, 2856, 1723, 1565, 1414, 1280, 1264, 1110, 778, 717, 698. MS (ES) m/e, 365. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found C, 72.83; H, 6.59; N, 7.62.

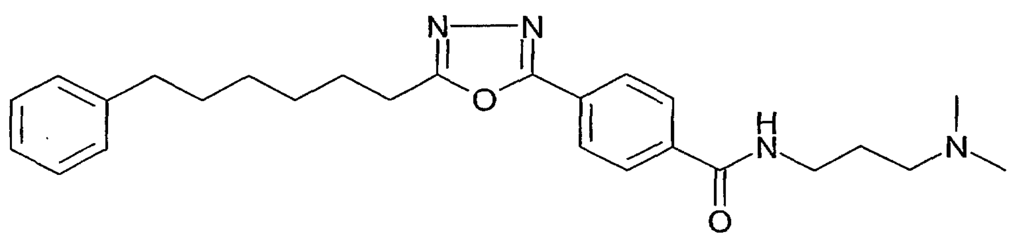
b) 4-[5—(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.676 g, 1.93 mmol) and lithium hydroxide (0.139 g, 5.79 mmol) to afford 0.616 g (95%) of 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 8.05-8.13 (m, 4H), 7.12-7.28 (m, 5H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H, J=8Hz), 1.72-1.82 (m, 2H), 1.50-1.63 (m, 2H), 1.26-1.46 (m, 4H). IR (KBr, cm^{-1}) 2942, 2924, 2853, 1686, 1573, 1429, 1287, 715. MS (ES) m/e, 351, 349. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found C, 71.59; H, 6.45; N, 7.86.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzamide

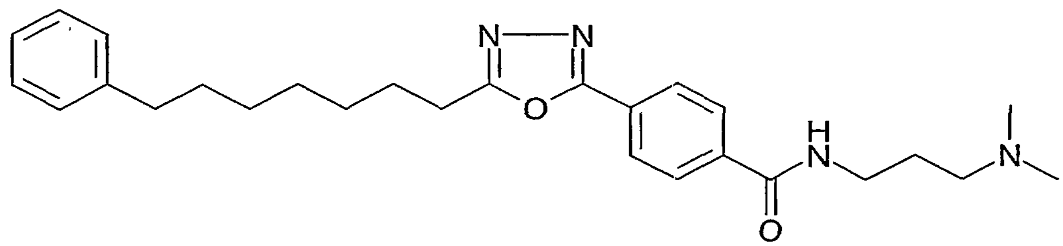


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzoic acid (0.488 g, 1.39 mmol), 1-hydroxybenzotriazole (0.188 g, 1.39 mmol), 4-dimethylamino pyridine (0.017 g, 0.14 mmol) and 3-(dimethylamino)propylamine (0.149 g, 1.46 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (eltuted with a 10% 2M ammonium :CH_2Cl_2) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.152 g (25%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzamide.

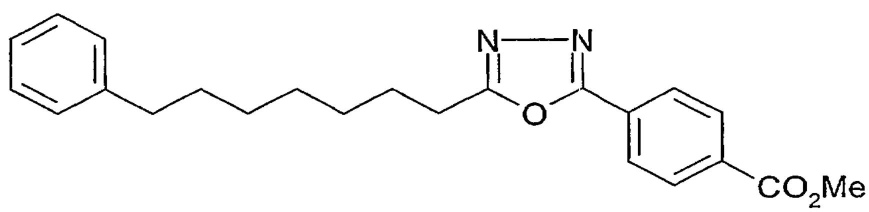
^{1}H NMR (DMSO-d6) δ 8.71 (t, 1H, J=5Hz), 8.00-8.08 (m, 4H), 7.12-7.238 (m, 5H), 3.31 (m, 2H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H, J=8Hz), 2.27 (t, 2H, J=7Hz), 2.13 (s, 6H), 1.53-1.79 (m, 6H), 1.30-1.44 (m, 4H). IR (KBr, cm^{-1}) 2936, 2861, 1652, 1586, 1567, 1556, 1529, 1495, 1302. MS (ES) m/e, 435, 433. Anal. Calcd for $C_{26}H_{34}N_4O_2$: C, 71.86; H, 7.89; N, 12.89. Found C, 71.59; H, 7.69; N, 12.72. Mp(°C)=91.

Example 13

Preparation of N-(3-dimethylaminopropyl)-4-(5-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzamide from 8-phenyloctanoic acid



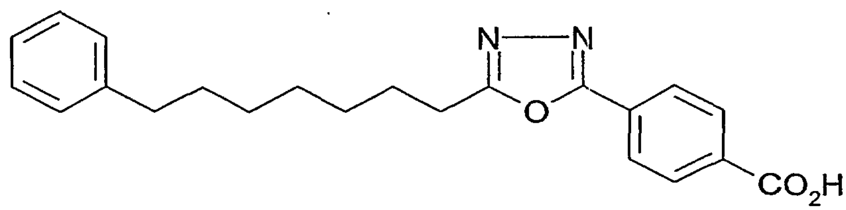
a) 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 8-phenyloctanoic acid (0.763 g, 3.46 mmol), 1,3-dicyclohexylcarbodiimide (0.714 g, 3.46 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.700 g, 3.43 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 25% to 50% EtOAc :hexane) followed by crystallization of the isolated material from diethyl ether afforded 0.522 g (40%) of 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.13 (m, 4H), 7.12-7.28 (m, 5H), 3.90 (s, 3H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.63-1.81 (m, 2H), 1.44-1.61 (m, 2H), 1.22-1.41 (m, 6H). IR (KBr, cm^{-1}) 2926, 1724, 1570, 1437, 1280, 1110,712. MS (ES) m/e, 379. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found C, 73.11; H, 7.08; N, 7.68.

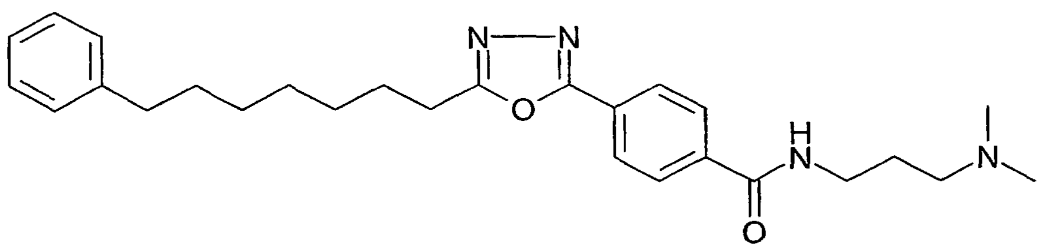
b) 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 4-[5-(3-phenyl heptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid methyl ester (0.467 g, 1.23 mmol) and lithium hydroxide (0.089 g, 3.70 mmol), in THF (5.4 mL) and water (1.0 mL) to afford 0.435 g (97%) of 4-[5-(3-phenylheptyl)-[1,3,4]- oxadiazol-2-yl)benzoic acid.

^{1}H NMR (DMSO-d6) δ 8.06-8.14 (m, 4H), 7.12-7.28 (m, 5H), 2.94 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7Hz), 1.69-1.81 (m, 2H), 1.50-1.61 (m, 2H), 1.23-1.41 (m, 6H). IR (KBr, cm^{-1}) 2928, 2922, 2850, 1688, 1585, 1571, 1434, 1321, 1291, 722. MS (ES) m/e, 365, 363. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found C, 69.19; H, 6.35; N, 7.47.

c) 4[5-(3-dimethylaminopropyl)-4-(5-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzamide

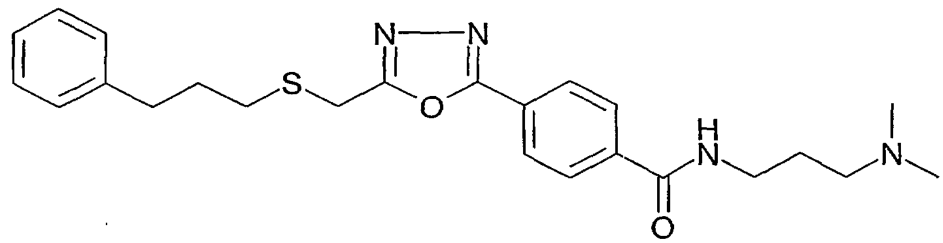


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(3-phenylheptyl)-[1,3,4]oxadiazol-2-yl)benzoic acid (0.399 g, 1.14 mmol), 1-hydroxybenzotriazole (0.154 g, 1.14 mmol), 4-dimethylamino pyridine (0.014 g, 0.11 mmol) and 3-(dimethylamino)propylamine (0.122 g, 1.20 mmol) to afford the title compound as a crude mixture. Purification by silica gel radial chromatography (eltuted with a 10% 2M ammonium: CH_2Cl_2) followed by crystallization of the isolated material from ethanol:diethyl ether afforded 0.103 g (20%) of 4[5-(3-dimethylaminopropyl)-4-(5-phenylhexyl)-[1,3,4]oxadiazol-2-yl)benzamide.

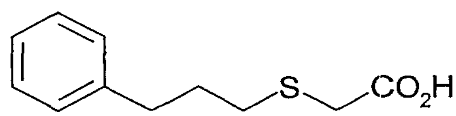
^{1}H NMR (DMSO-d6) δ 8.71 (t, 1H, J=5Hz), 8.00-8.08 (m, 4H), 7.12-7.28 (m, 5H), 3.32 (m, 2H), 2.93 (t, 2H, J=7Hz), 2.56 (t, 2H,J=8Hz), 2.26 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.44-1.77 (m, 6H), 1.27-1.40 (m, 6H). IR ($CHCl_3$, cm^{-1}) 3008, 2934, 2859, 2827, 1652, 1586, 1556, 1495. MS (ES) m/e, 449. Anal. Calcd for $C_{27}H_{36}N_4O_2$: C, 72.29; H, 8.09; N, 12.49. Found C, 72.21; H, 8.05; N, 12.50. Mp(°C)=108.

Example 14

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 3-phenylpropylmercaptan



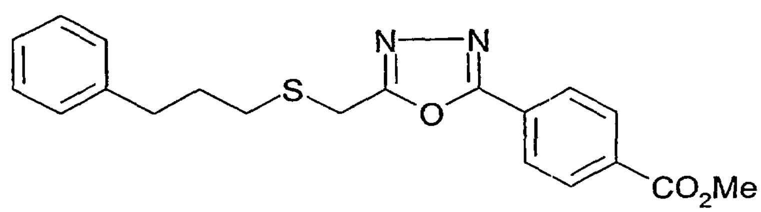
a) (3-phenylpropylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1a, from 3-phenylpropylmercaptan (3.13 g, 20.6 mmol), sodium hydride (0.823 g, 20.6 mmol), and methyl bromoacetate (2.86 g, 18.7 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 4 x 250 mL 15% EtOAc:hexane followed by 3 x 250 mL EtOAc) afforded 3.83 g, (89%) of (3-phenylpropylsulfanyl)acetic acid.

^{1}H NMR (DMSO-d6) δ 12.51 (bs, 1H), 7.15-7.30 (m, 5H), 3.23 (s, 2H), 2.65 (t, 2H, J=8Hz), 2.58 (t, 2H, J=7Hz), 1.78-1.88 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3029, 3011, 1710, 1601, 1454, 1423, 1295, 1197. MS (ES) m/e, 209. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found C, 62.70; H, 6.52.

b) 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

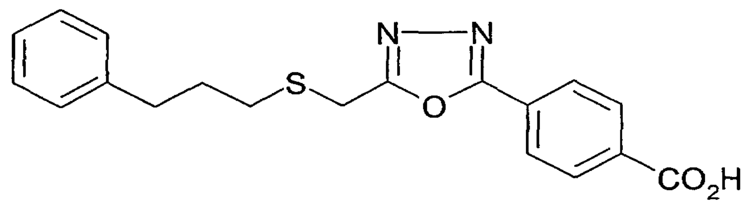


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (3-phenylpropylsulfanyl)acetic acid (0.975 g, 4.6 nM), 1,3-dicyclohexylcarbodiimide (0.957 g, 4.6 mmol), and 4-(1*H*-tetrazole-5-yl)benzoic acid

methyl ester (0.789 g, 3.9 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel followed by crystallization from diethyl ether afforded a total of 0.668 g (47%) of 4-[5-(3-phenylpropylsulfanylmethyl) [1,3,4]oxadiazol-2-yl] benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.09-8.18 (m, 4H), 7.12-7.26 (m, 5H), 4.14 (s, 2H), 3.91 (s, 3H), 2.62-2.67 (m, 4H), 1.80-1.90 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1721, 1554, 1438, 1299, 1283, 1119, 1111. MS (ES) m/e, 369. Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found C, 65.05; H, 5.48; N, 7.67.

c) 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



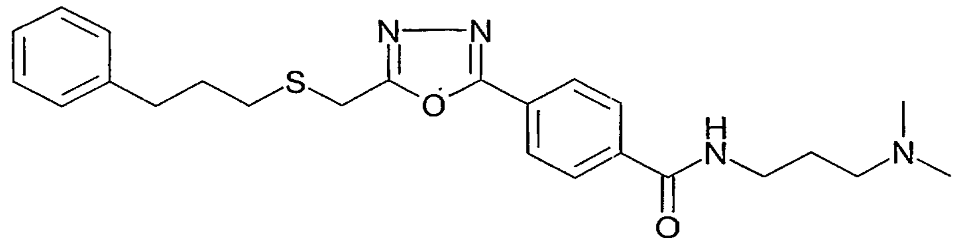
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.600 g, 1.63 mmol) and lithium hydroxide (0.117 g, 4.89 mmol) to afford 0.522 g (90%) of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

^{1}H NMR (DMSO-d6) δ 8.03-8.16 (m, 4H), 7.11-7.28 (m, 5H), 4.14 (s, 2H), 2.66 (dt, 4H, J=7Hz), 1.79-1.88 (m, 2H).

IR (KBr, cm^{-1}) 1706, 1685, 1551, 1433, 1324, 1293, 715, 699.

MS (ES) m/e, 355,353. Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found C, 63.29; H, 4.95; N, 7.81.

d) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

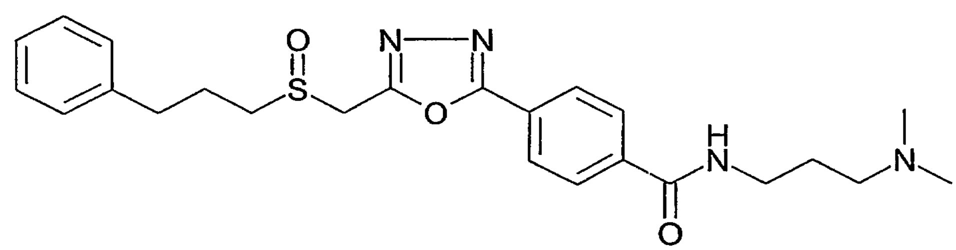


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.492 g, 1.39 mmol), 1,1'-carbonyldiimidazole (0.236 g, 1.46 mmol) and 3-(dimethylamino)propylamine (0.170 g, 1.67 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M ammonia in MeOH:$CHCl_3$) afforded 0.392 g (64%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

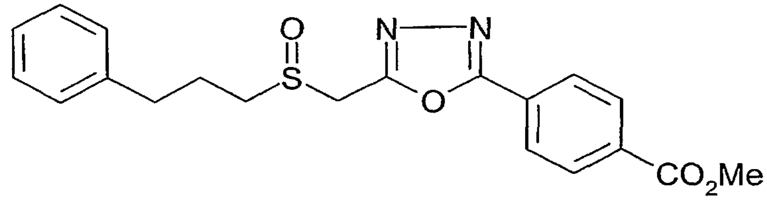
^{1}H NMR (DMSO-d6) δ 8.72 (t, 1H, J=5Hz), 8.01-8.07 (m, 4H), 7.12-7.26 (m, 5H), 4.13 (s, 2H), 2.62-2.67 (m, 4H), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.75-1.86(m, 2H), 1,63-1.72 (m, 2H). IR (KBr, cm^{-1}) 3338, 2939, 2813, 2761, 1638, 1581, 1552, 1534, 1496, 1456, 1288, 712. MS (ES) m/e, 439, 437. Anal. Calcd for $C_{24}H_{30}N_4O_2S$: C, 65.73; H, 6.89; N, 12.77. Found C, 65.82; H, 6.94; N, 12.74. Mp(°C)=112.

Example 15

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



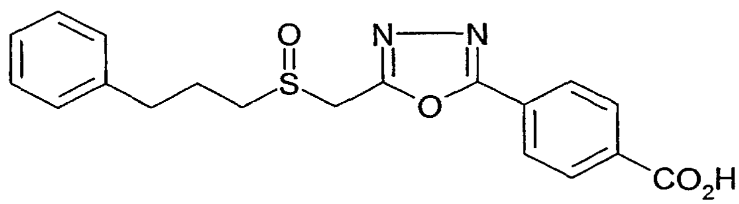
a) 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



A solution of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.870 g, 2.4 mmol) in 12 mL CH_2Cl_2 stirring at 0 °C was added dropwise and peracetic acid (0.673 g, 2.8 mmol). After 2.1 hours the mixture was stirred at room temperature for 20 minutes before additional peracetic acid (0.036 g, 0.47 mmol) was added. Fifty minutes later additional peracetic acid (0.036 g, 0.47 mmol) was added. Twenty minutes after the second addition, the reaction was quenched with 5 mL saturated aqueous solution of sodium sulfite. The mixture was diluted with water then extracted with CH_2Cl_2. The organic phase was washed twice with H_2O, once with brine, dried over sodium sulfate, filtered, concentrated to afford a solid. Crystallization form acetone afforded 0.660 g (73%) of 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.11-8.20 (m, 4H), 7.16-7.32 (m, 5H), 4.73-4.78 (m, 1H), 4.51-4.56 (m, 1H), 3.90 (s, 3H), 2.88-3.05 (m, 2H), 2.72-2.77 (m, 2H), 1.95-2.05 (m, 2H). IR ($CHCl_3$, cm^{-1})1722, 1551, 1438, 1283, 1111. MS (ES) m/e, 385. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25. Found C, 62.11; H, 5.22; N, 7.31.

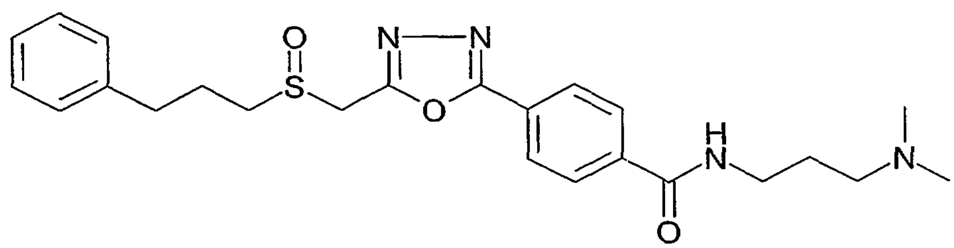
b) 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.599 g, 1.56 mmol) and lithium hydroxide (0.112 g, 4.67 mmol) to afford 0.457 g (79%) of 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.40 (bs, 1H), 8.03-8.17 (m, 4H), 7.16-7.23 (m, 5H), 4.75 (d, 1H, J=14Hz), 4.54 (d, 1H, J=14Hz), 2.88-3.05 (m, 2H), 2.70-2.80 (m, 2H), 1.96-2.09 (m,2H). IR (KBr, cm^{-1}) 2923, 1706, 1685, 1554, 1434, 1324, 1292, 1044, 1012, 873, 716, 697. MS (ES) m/e, 371. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found C, 60.74; H, 4.79; N, 7.43.

c) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

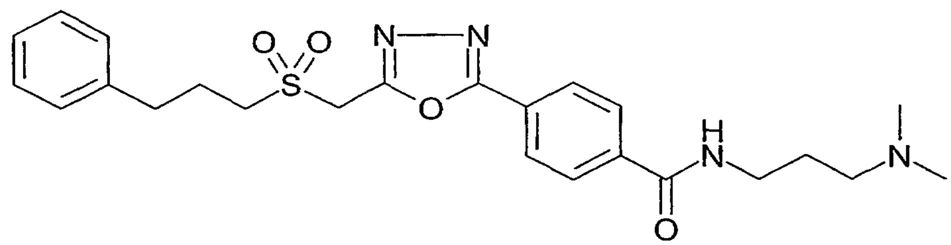


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropane-1-sulfinylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid (0.448 g, 1.20 mmol), 1,1'-carbonyldiimidazole (0.205 g, 1.26 mmol) and 3-(dimethylamino)propylamine (0.147 g, 1.44 mmol) to afford the title compound as a crude mixture. Crystallization of the crude material from methanol:diethyl ether afforded 0.284 g (45%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfinylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

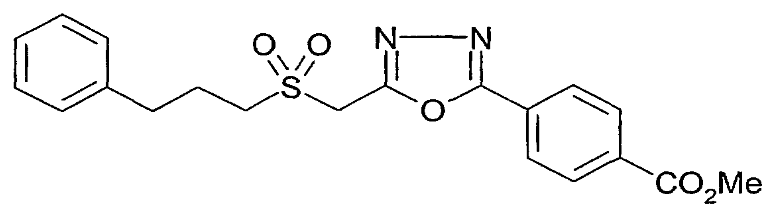
^{1}H NMR (DMSO-d6) δ 8.73 (t, 1H, J=5Hz), 8.05 (m, 4H), 7.17-7.32 (m, 5H), 4.73 (d, 1H, J=14Hz), 4.52 (d, 1H, J=14Hz), 3.32 (m, 2H), 2.84-3.03 (m, 2H), 2.62-2.70 (m, 2H), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.94-2.06 (m, 2H), 1.62-1.72 (m, 2H). IR (KBr, cm^{-1}) 3334, 1645, 1585, 1554, 1536, 1304, 1047, 859 MS (ES) m/e, 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65; N, 12.32. Found C, 62.86; H, 6.58; N, 12.14. Analytical HPLC: 100% Purity. Mp(°C)=127.

Example 16

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



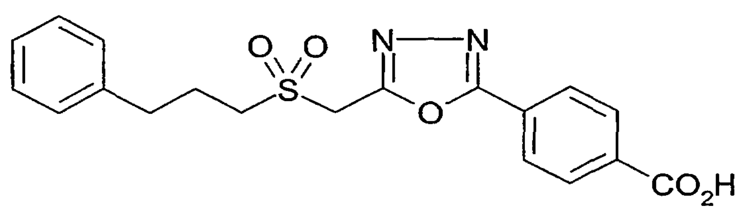
a) 4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



A solution of 4-[5-(3-phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.970 g, 2.63 mmol) and m-chloroperoxybenzoic acid (1.82 g, 5.8 mmol) in 14 mL CH_2Cl_2 was stirred at room temperature for 4.5 hours. The mixture was then quenched with 5 mL saturated aqueous solution of sodium sulfite. The mixture was diluted with water then extracted with CH_2Cl_2. The organic phase was washed twice with H_2O, once with brine, dried over sodium sulfate, filtered, concentrated to afford a solid. Crystallization form acetone afforded 0.733 g (70%) of 4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.11-8.20 (m, 4H), 7.18-7.33 (m, 5H), 5.25 (s, 2H), 3.91 (s, 3H), 3.38 (t, 2H, J=8Hz), 2.74 (t, 2H, J=8Hz), 2.02-2.13 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1722, 1438, 1333, 1299, 1284, 1112. MS (ES) m/e, 401, 399. Anal. Calcd for $C_{20}H_{20}N_2O_5S$: C, 59.99; H, 5.03; N, 7.00. Found C, 59.93; H, 5.12; N, 6.95.

b) 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid

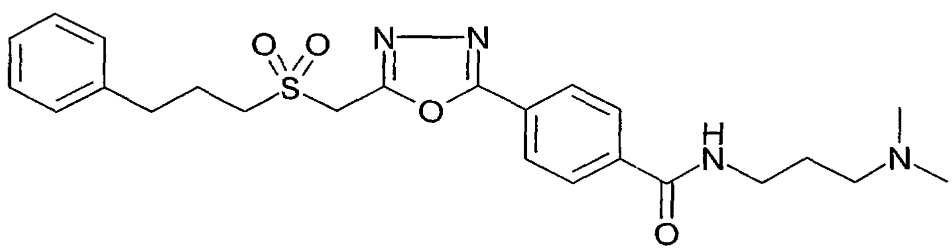


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(3-phenylpropane-1-sulfonylmethyl)-

[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.667 g, 1.67 mmol) and lithium hydroxide (0.120 g, 5.00 mmol) to afford 0.559 g (87%) of 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid.

^{1}H NMR (DMSO-d6) δ 13.38 (bs, 1H), 8.08-8.18 (m, 4H), 7.18-7.34 (m, 5H), 5,25 (s, 2H), 3.38 (t, 2H, J=8Hz), 2.75 (t, 2H, J=8Hz), 2.01-2.13 (m, 2H). IR (KBr, cm^{-1}) 2995, 2675, 2555, 1706, 1685, 1551, 1433, 1321, 1294, 1137, 1131, 1121, 717. MS (ES) m/e, 387. Anal. Calcd for $C_{19}H_{18}N_2O_5S$: C, 59.06; H, 4.70; N, 7.25. Found C, 58.42; H, 4.69; N, 7.11.

c) N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

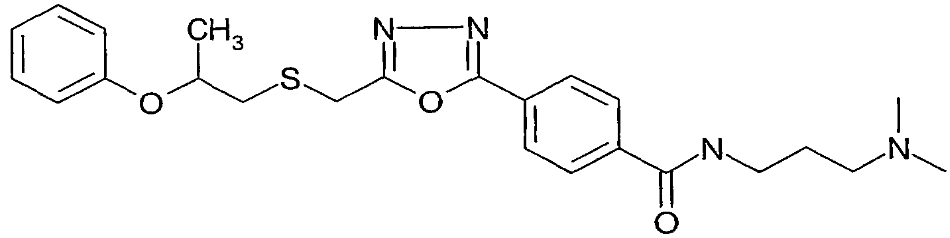


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(3-phenylpropane-1-sulfonylmethyl)[1,3,4]oxadiazol-2-yl]benzoic acid (0.550 g, 1.42 mmol), 1,1'-carbonyldiimidazole (0.242 g, 1.49 mmol) and 3-(dimethylamino)propylamine (0.175 g, 1.71 mmol) to afford the title compound as a crude mixture. Crystallization of the crude material from methanol:diethyl ether afforded 0.378 g (56%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenylpropane-1-sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

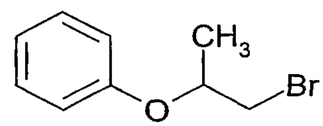
^{1}H NMR (DMSO-d6) δ 8.74 (t, 1H, J=5Hz), 8.05 (m, 4H), 7.18-7.34 (m, 5H), 5.23 (s, 2H), 3.28-3.40 (m, 4H), 2.74 (t, 2H, J=8Hz), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 2.02-2.10 (m, 2H), 1.63-1.72 (m, 2H). IR (KBr, cm^{-1}) 3264, 2941, 2763, 1634, 1555, 1320, 1166, 1115, 697. MS (ES) m/e, 469. Anal. Calcd for $C_{24}H_{30}N_4O_4S$: C, 61.26; H, 6.43; N, 11.91. Found C, 61.38; H, 6.52; N, 11.94. Mp(°C)=157.

Example 17

Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 2-phenoxypropanol



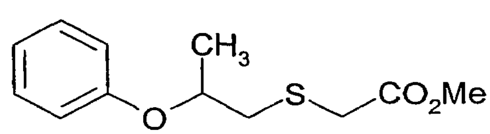
a) (2-Bromo-1-methylethoxy)benzene



A solution of triphenylphosphine (8.63 g, 32.9 mmol) in 94 mL CH_2Cl_2 stirring at room temperature was added dropwise, bromine (5.26 g, 32.9 mmol) over a twenty minute period. The resultant suspension was stirred at room temperature for 15 minutes then a solution of 2-phenoxypropanol (5.01 g, 32.9 mmol) and imidazole (2.69 g, 39.5 mmol) in 70 mL CH_2Cl_2 was added over a 15 minute period. The mixture was stirred at room temperature for 2.5 hours then subjected to filtration. The filtrate was concentrated in vacuo to afford an oil. Purification by flash filtration chromatography on silica gel (elution with 15%EtOAc:hexane) afforded 4.80 g (68%) of (2-Bromo-1-methylethoxy)benzene.

^1H NMR (DMSO-d6) δ 7.32-7.39 (m, 2H), 6.92-6.99 (m, 3H), 4.63-4.72 (m, 1H), 3.69 (ddd, 2H, J=5, 11 and 22Hz), 1.33 (d, 3H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 1600, 1588, 1495, 1062. MS (ES) m/e, 214. Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15. Found C, 44.83; H, 4.51.

b) (2-Phenoxypropylsulfanyl)acetic acid methyl ester

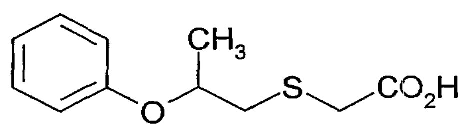


A solution of methyl thioglycolate (1.64 g, 15.4 mmol) in 61 mL THF stirring at room temperature was added sodium hydride (0.62 g, 15.4 mmol). The mixture was stirred fifteen minutes before a solution of 2-bromo-1-methylethoxy)benzene (3.02 g, 14.0

mmol) in 3.0 mL THF was added. The mixture was stirred at room temperature for two days. The reaction mixture was diluted with 100 mL EtOAc then washed three times with water, brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with a linear gradient of 10 to 25% Et_2O:hexane) afforded 2.20 g (65%)(2-phenoxypropylsulfanyl)acetic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 7.24-7.30 (m, 2H), 6.90-6.94 (m, 3H), 4.60-4.66 (m, 1H), 3.61 (s, 3H), 3.45 (d, 2H, J=3Hz), 2.76 (ddd, 2H, J=6, 14, 38Hz), 1.30 (d, 3H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 1735, 1599, 1587, 1495, 1438, 1289, 1173, 1132. MS (ES) m/e, 241. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found C, 49.24; H, 5.39.

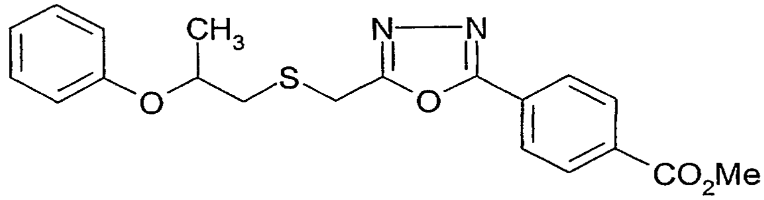
c) (2-Phenoxypropylsulfanyl)acetic acid



A mixture of 2-phenoxypropylsulfanyl)acetic acid methyl ester (1.93 g, 8.0 mmol) and lithium hydroxide (0.577 g, 24.1 mmol) was stirred at room temperature for 5.5 hours. The reaction mixture was quenched with concentrated HCl (2.02 mL, 8.0 mmol), diluted with EtOAc and water. The phases were separated and the aqueous phase extracted once with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, concentrated to afford 1.22 g (67%) of (2-Phenoxypropylsulfanyl)acetic acid.

^{1}H NMR (DMSO-d6) δ 7.24-7.31 (m, 2H), 6.89-6.96 (m, 3H), 4.59-4.69 (m, 1H), 3.28-3.39 (m, 2H), 2.76-2.95 (m, 2H), 1.30 (d, 3H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 2982, 2931, 1711, 1599, 1587, 1495, 1291, 1239, 1173, 1131. MS (ES) m/e, 227, 225. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24. Found C, 58.80; H, 6.00.

d) 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester

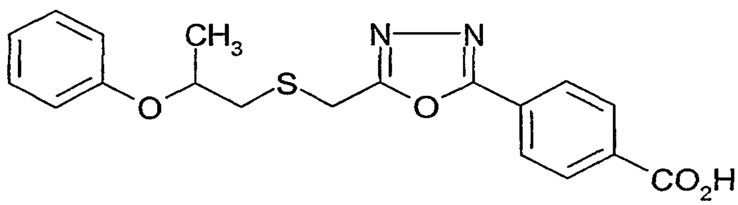


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (2-phenoxypropylsulfanyl)acetic acid (0.950 g, 4.2 nM), 1,3-dicyclohexylcarbodiimide (0.866 g, 4.2 mmol), and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (0.857 g, 4.2 mmol) to afford the title compound as a crude mixture. Purification three times by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.631 g (39%) of 4-[5-(2-phenoxypropyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as an oil that slowly crystallized out.

^{1}H NMR (DMSO-d6) δ 8.07-8.16 (m, 4H), 7.20-7.27 (m, 2H), 6.86-6.94 (m, 3H), 4.62-4.68 (m, 1H), 4.16-4.27 (m, 2H), 3.91 (s, 3H), 2.89-2.95 (m, 2H), 1.29 (d, 2H, J=6Hz).

MS (ES) m/e, 385. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found C, 62.25; H, 5.00; N, 6.71.

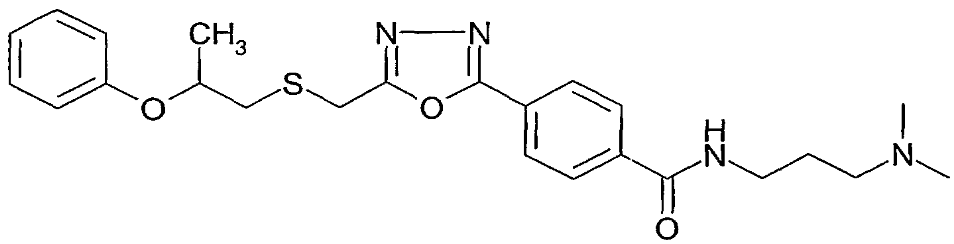
e) 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (0.611 g, 1.59 mmol) and lithium hydroxide (0.114 g, 4.76 mmol) to afford 0.573 g (97%) of 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid.

^{1}H NMR (DMSO-d6) δ13.35 (bs, 1H) 8.04-8.14 (m, 4H), 7.21-7.30 (m, 3H), 6.87-6.94 (m, 3H), 4.58-4.71 (m, 2H), 4.16-4.27 (m, 2H), 2.88-3.00 (m, 2H), 1.29 (d, 3H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 1700, 1587, 1495, 1240. MS (ES) m/e, 371, 369.

f) N-(3-dimethylaminopropyl)-4-[5-(2-phenoxypropyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

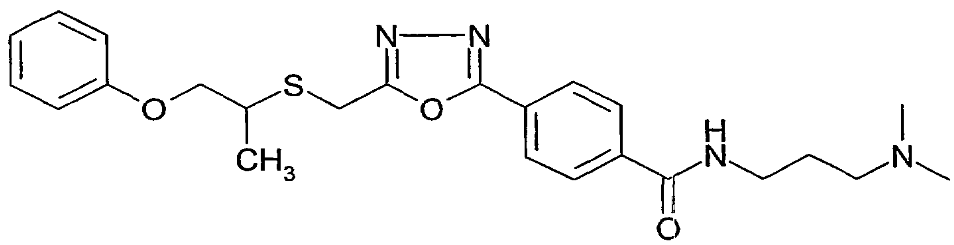


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(2-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.541 g, 1.46 mmol), 1,1'-carbonyldiimidazole (0.249 g, 1.53 mmol) and 3-(dimethylamino)propylamine (0.157 g, 1.53 mmol) to afford the title compound as a crude material. Purification by silica gel radial chromatography (elution with 10% 2M NH_3 in $MeOH:CH_2Cl_2$) followed by treatment of the isolated material with oxalic acid in acetone afforded the oxalate salt of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxy propylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

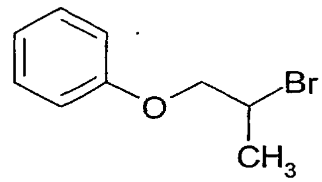
^{1}H NMR (DMSO-d6) δ 8.85 (t, 1H, J=6Hz), 8.04 (s, 4H), 7.18-7.27 (m, 2H), 6.87-6.93 (m, 3H), 4.63-4.69 (m, 1H), 4.16-4.27 (m, 2H), 3.32-3.39 (q, 2H, J=6Hz), 3.00-3.10 (m, 2H), 2.87-2.98 (m, 2H), 2.75 (s, 6H), 1.86-1.95 (m, 2H), 1.29 (d, 2H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 3009, 1778, 1656, 1599, 1586, 1495, 1302, 1239, 1012. MS (ES) m/e, 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S \cdot C_2H_2O_4$: C, 57.34; H, 5.92, N, 10.29. Found C, 56.92; H, 5.81; N, 10.22. Mp(°C)=117.

Example 18

Preparation of N-(3-dimethylaminopropyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from 1-phenoxy-2-propanol



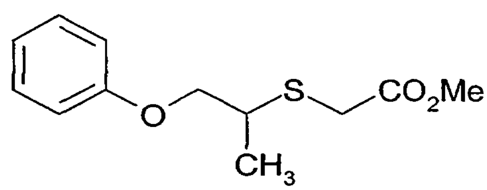
a) (2-bromopropoxy)benzene



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17a, from 1-phenoxy-2-propanol (7.01 g, 46.1 mmol)(containing approximately 10% 2-phenoxypropanol), triphenylphosphine (12.08 g, 46.1 mmol), bromine (7.36 g, 46.1mM) and imidazole (3.76 g, 55.3 mmol) to afford 9.23 g (93%) of (2-bromopropoxy)benzene as an oil which is contaminated with approximately 10% (2-bromo-1-methylethoxy)benzene.

^{1}H NMR (DMSO-d6) δ 7.26-7.33 (m, 2H), 6.92-6.98 (m, 3H), 4.47-4.56 (m, 1H), 4.13-4.24 (m, 2H), 1.72 (d, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 15600, 1588, 1497, 1244, 1035. MS (ES) m/e, 216, 214. Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15. Found C, 41.53; H, 4.64.

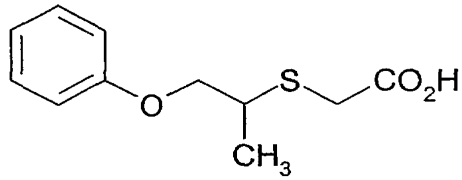
b) (1-Methyl-2-phenoxyethylsulfanyl)acetic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from (2-bromopropoxy)benzene (3.90 g, 18.1 mmol), methylthioglycolate (2.12 g, 19.9 mmol), and sodium hydride (0.798 g, 19.9 mmol) to afford 2.30 g (53%) of (1-Methyl-2-phenoxyethylsulfanyl) acetic acid methyl ester as an oil.

^{1}H NMR (DMSO-d6) δ 7.25-7.32 (m, 2H), 6.90-6.96 (m, 3H), 4.10 (dd, 1H, J=6,10Hz), 3.94 (dd, 1H, J=7, 10Hz), 3.44-3.62 (m, 5H), 3.24-3.31 (m, 1H), 1.29 (d, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 1735, 1600, 1497, 1289, 1243. MS (ES) m/e, 241. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found C, 59.61; H, 6.63.

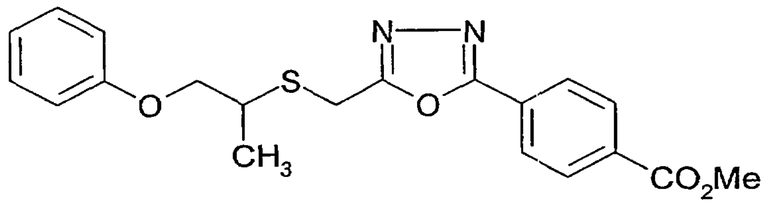
c) (1-Methyl-2-phenoxyethylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from (1-Methyl-2-phenoxyethylsulfanyl)acetic acid methyl ester (2.01 g, 8.36 mmol) and lithium hydroxide (0.601 g, 25.1 mmol) to afford 1.84 g (97%) of (1-Methyl-2-phenoxyethylsulfanyl)acetic acid as an oil.

^{1}H NMR (DMSO-d6) δ 12.51 (bs, 1H), 7.24-7.32 (m, 2H), 6.90-6.95 (m, 3H), 4.11 (dd, 1H, J=5, 10Hz), 3.93 (dd, 1H, J=7, 10Hz), 3.23-3.48 (m, 3H), 1.33 (d, 3H, J=11Hz). IR ($CHCl_3$, cm^{-1}) 3010, 1712, 1600, 1587, 1497, 1300, 1291, 1243. MS (ES) m/e, 225. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24. Found C, 58.34; H, 6.08.

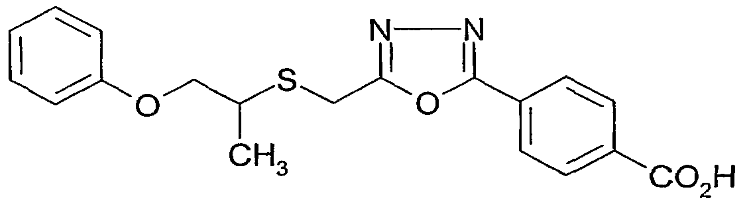
d) 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (1-Methyl-2-phenoxyethylsulfanyl)acetic acid (1.44 g, 6.4 nM), 1,3-dicyclohexylcarbodiimide (1.31 g, 6.4 mmol), and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (1.30 g, 6.4 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 1.21 g (49%) of 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as an oil that crystallizes out.

^{1}H NMR (DMSO-d6) δ 8.07-8.16 (m, 4H), 7.20-7.31 (m, 2H), 6.89-6.96 (m, 3H), 4.29 (m, 2H), 4.11-4.15 (m, 1H), 4.00 (dd, 1H, J=7, 10Hz), 3.91 (s, 3H), 3.21-3.33 (m, 1H), 1.33 (d, 3H, J=7Hz). MS (ES) m/e, 385, 383. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24, N, 7.29. Found C, 63.52; H, 5.95; N, 6.91.

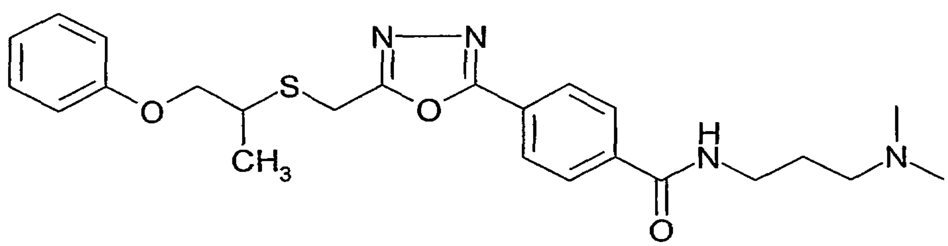
e) 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester (1.19 g, 3.1 mmol), and lithium hydroxide (0.222 g, 9.3 mmol) to afford 1.06 g (92%) of (4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a solid.

^{1}H NMR (DMSO-d6) δ 13.36 (bs, 1H), 8.05-8.14 (M, 4h), 7.20-7.28 (m, 2H), 6.88-6.96 (m, 3H), 4.22-4.37 (m, 2H), 4.13 (dd, 1H, J=6, 10Hz), 4.00 (dd, 1H, J=6,10Hz), 3.25-3.37 (m, 1H), 1.34 (d, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 3010, 2934, 2859, 1700, 1600,1587, 1497, 1286, 1266, 1242. MS (ES) m/e, 371, 369.

f) N-(3-dimethylaminopropyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide

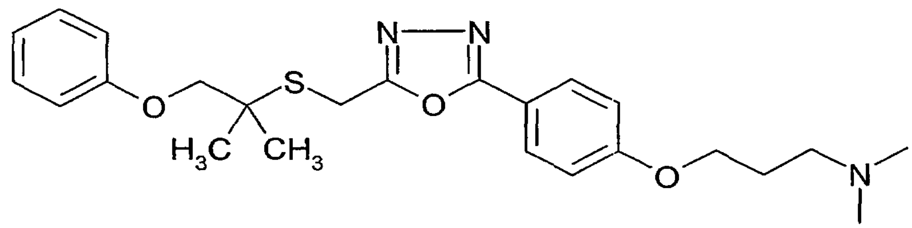


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1d, from 4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (1.04 g, 2.8 mmol), 1,1'-carbonyldiimidazole (0.477 g, 2.9 mmol) and 3-(dimethylamino)propylamine (0.301 g, 2.9 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:CH_2Cl_2) followed by crystallization with EtOH:Et2O afforded 0.404 g (32%) of N-(3-dimethylamino propyl)-4-[5-(1-methyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide.

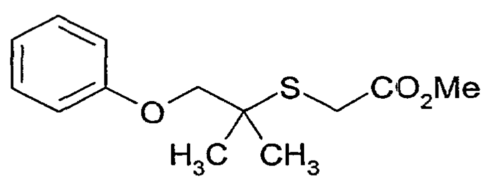
^{1}H NMR (DMSO-d6) δ 8.72 (t, 1H, J=5Hz), 7.99-8.06 (m, 4H), 7.23-7.28 (m, 2H), 6.89-6.94 (m, 3H), 4.22-4.37 (m, 2H), 4.14 (dd, 1H, J=6 and 10Hz), 4.01 (dd, 1H, J=7 and 10Hz), 3.27-3.38 (m, 4H), 2.27 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.72 (m, 2H), 1.33 (d, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 307, 2951, 2827, 1652, 1585, 1550, 1496, 1243, 1012. MS (ES) m/e, 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65, N, 12.32. Found C, 63.57; H, 6.62; N, 12.28. Mp(°C)=84.

Example 19

Preparation of 3—{4-[5-1,1-dimethyl-2-phenoxyethyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl) dimethylamine from isobutylene sulfide



a) (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester

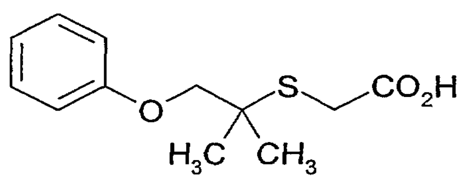


A suspension of sodium hydride (0.416 g, 10.4 mmol) (washed twice with hexane) in 30 mL THF stirring at room temperature was added dropwise a solution of phenol (0.978 g, 10.4 mmol) in 3.5 mL THF. The resultant solution was added to a suspension of chloro(triphenylphosphine)gold (5.14 g, 10.4 mmol) in 30 mL THF over an 80 minute period. The temperature of the mixture was maintained between –30 °C and 10 °C (dry ice/CH_3CN) during the addition of the sodium phenolate. The reaction was then stirred at room temperature for 3.5 hours before isobutylene sulfide (0.962 g, 10.9 mmol) was added. The reaction continued stirring at room temperature for approximately 4 hours then methyl boromacetate (1.75 g, 11.4 mmol) was added. The reaction was stirred overnight at room temperature. The suspension was treated with Celite, filtered through a pad of Celite and rinsed with diethyl ether. The filtrate was concentrated to an oil which

slowly turns into a suspension. The suspension was diluted with hexane, filtered and the filtrate concentrated to a yellow oil. Purification by chromatography on silica gel (elution with CH_2Cl_2) afforded 1.66 g (54%) of (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester a yellow oil.

^{1}H NMR (DMSO-d6) δ 7.26-7.31 (m, 2h), 6.91-6.96 (m, 3H), 3.91 (s, 2H), 3.57 (s, 3H), 3.51 (s, 2H), 1.35 (s, 6H).
IR ($CHCl_3$, cm^{-1}) 3004, 2954, 2932, 2869, 1736, 1600, 1498, 1466, 1290, 1245, 1172, 1135. MS (ES) m/e, 255. Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found C, 61.40; H, 7.17.

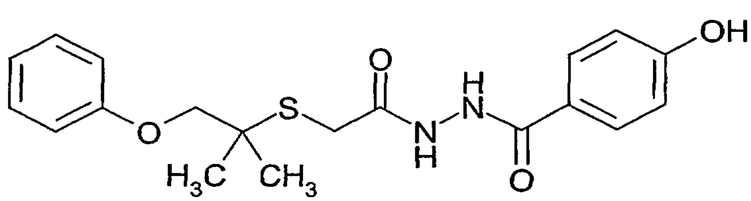
b) (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7b, from 1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid methyl ester (1.85 g, 7.3 mmol), lithium hydroxide (0.522 g, 21.8 mmol) to afford 1.28 g (73%) of (1,1-dimethyl-2-phenoxyethyl sulfanyl) acetic acid as an oil.

^{1}H NMR (DMSO-d6) δ 7.25-7.31 (m, 2H), 6.91-6.95 (m, 3H), 3.92 (s, 2H), 3.40 (s, 2H), 1.35 (s, 6H).IR ($CHCl_3$, cm^{-1}) 2969, 2930, 2871, 1713, 1600, 1587, 1498, 1466, 1301, 1291, 1245, 1173. MS (ES) m/e, 240, 239. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found C, 43.43; H, 4.94.

c) 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethyl sulfanyl)acetyl]hydrazide

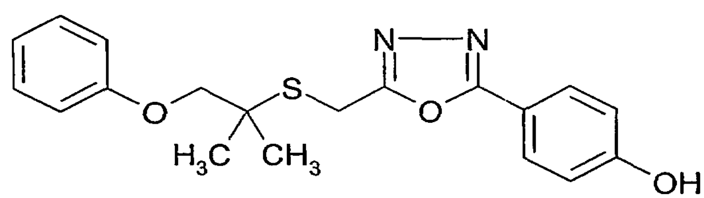


A solution of (1,1-dimethyl-2-phenoxyethylsulfanyl) acetic acid (1.19 g, 4.95 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.22 g, 4.95 mmol)in 25 mL

CH_3CN and 6 mL THF was stirred at room temperature for 1 hour. The mixture was then treated with 4-hydroxybenzoic hydrazide (0.753 g, 4.95mM). The suspension was stirred at room temperature for 28 hours. The suspension was filtered, insolubles rinsed with CH_3CN and the filtrate concentrated to an oil. Purification by chromatography on silica gel (elution with 50% EtOAc:hexane followed by 75%EtOAc:hexane) afforded 0.910 g(49%) of 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethylsulfanyl)acetyl]hydrazide as a white foam.

^1H NMR (DMSO-d6) δ 9.98-10.15 (m, 2H), 7.75 (d, 2H, J=9Hz), 7.25-7.31 (m, 2H), 6.91-7.00 (m, 3H), 6.81 (d, 2H, J=9Hz), 3.96 (s, 2H), 3.40 (s, 2H), 1.39 (s, 6H). IR ($CHCl_3$, cm^{-1}) 1685, 1632, 1610, 1600, 1588, 1498, 1467, 1456, 1245, 1172. MS (ES) m/e, 375, 373. Anal. Calcd for $C_{19}H_{22}N_2O_4S$: C, 60.94; H, 5.92, N, 7.48. Found C, 60.76; H, 5.91; N, 7.24.

d) 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenol

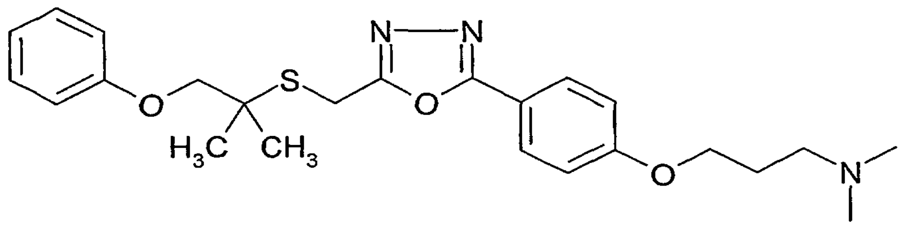


A mixture of 4-Hydroxybenzoic acid-N-[2-(1,1-dimethyl-2-phenoxyethylsulfanyl)acetyl]hydrazide (0.860 g, 2.3 mmol), triphenylphosphine (1.21 g, 4.6 mmol), triethyl amine (0.837 g, 8.3 mmol) and carbon tetrachloride (1.45 g, 8.3 mmol) in 24 mL CH_3CN was stirred at room temperature for 6.25 hours. The mixture was then concentrated to an oil. The oil was dissolved into EtOAc and washed three times with water and once with brine. The organic phase was dried over sodium sulfate, filtered, concentrated in vacuo to afford an oil. Purification by silica gel chromatography (elution with a linear gradient of 0 to 5% methanol:$CHCl_3$ over a twenty minute period) afforded 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol and triphenyl phosphine oxide as an oil that slowly crystallizes out. The mixture was duiluted with diethyl ether then filtered. The filtrate was concentrated to an oil. Purification by slicia gel radial chromatography (elution with 50% Et_2O:hexane) followed by

crystallization from MeOH:Et_2O afforded 0.499 g (61%) of 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.30 (bs, 1H), 7.76 (m, 2H), 7.73 (m, 2H), 7.21-7.28 (m, 2H), 6.90-6.94 (m, 3H), 4.23 (s, 2H), 3.96 (s, 2H), 1.40 (s, 6H). IR (KBr,cm^1) 3158, 1610, 1598, 1588, 1499, 1467, 1286, 1244, 1173, 757. MS (ES) m/e, 357, 355. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found C, 63.91; H, 5.65; N, 7.77.

e) 3-{4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)- [1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



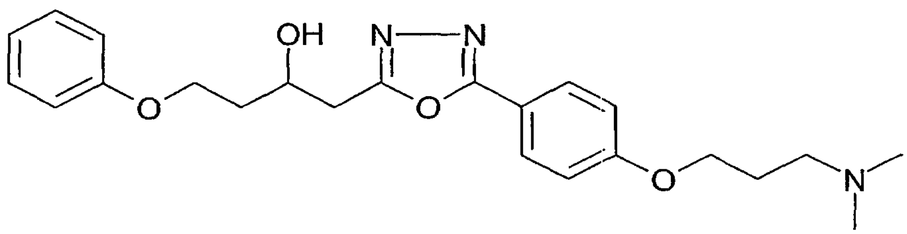
To a solution of 4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.205 g, 1.3 mmol) in 16.4 mL DMF stirring at room temperature was added sodium hydride (0.109 g, 2.7 mmol). The mixture was stirred 5 minutes then 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.205 g, 1.3 mmol) was added. The reaction was heated at 100 °C for 1.45 hours. After cooling to room temperature, the mixture was diluted with 50% EtOAc:hexane and 50% brine:H_2O. The phases were separated and the aqueous phase was extracted with 50% EtOAc:hexane. The combined organic phases were washed with 50% brine:H_2O the brine. The organic phase was dried over sodium sulfate, filtered, concentrated to afford 0.533 g an oil. The oil was dissolved into diethyl ether. To this solution was added dropwise a solution of EtOH in Et_2O that was treated with 0.103 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.154 g (27%) of 3—{4-[5-1,1-dimethyl-2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the hydrochloride salt.

^{1}H NMR (DMSO-d6) δ 7.86-7.88 (m, 2H), 7.210-7.28 (m, 2H), 7.10-7.15 (m, 2H), 6.90.-6.94 (m, 3H), 4.25 (s, 2H), 4.16 (t, 2H, J=6Hz), 3.96 (s, 2H), 3.19-3.24 (m, 2H), 2.79 (s, 6H), 2.13-2.22 (m, 2H), 1.40 (s, 6H). IR ($CHCl_3$, cm^{-1}) 2970, 1615, 1500,

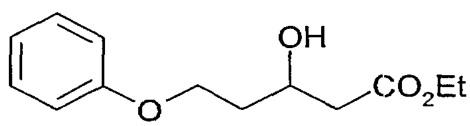
1245, 1224, 1175. MS (ES) m/e, 442. Anal. Calcd for $C_{24}H_{31}N_3O_3S{\cdot}HCl$: C, 60.30; H, 6.75; N, 8.79. Found C, 59.96; H, 6.59; N, 8.64. Mp(°C)=134.

Example 20

Preparation of 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol from 3-Oxo-5-phenoxypentanoic acid ethyl ester



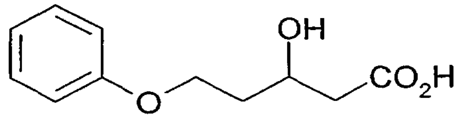
a) 3-hydroxy-5-phenoxypentanoic acid ethyl ester



A solution of 3-Oxo-5-phenoxypentanoic acid ethyl ester 910.23 g, 43.3 mmol) in 122 mL EtOH and sodium borohydride (0.573 g, 15.2 mmol) was stirred at room temperature for 2.0 hours. The mixture was then treated with H_2O and reduced in volume. EtOAc and 1N HCl were added, phases separated and the organic phase was washed with brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by HPLC on silica gel (elution with a linear gradient of 20 to 35% EtOAc:hexane over a 30 minute period) afforded 6.55 g (63%) of 3-hydroxy-5-phenoxypentanoic acid ethyl ester as an oil.

^1H NMR (DMSO-d6) δ 7.24-7.31 (m, 2H), 6.88-6.93 (m, 3H), 4.90 (d, 1H, J=6Hz), 3.94-4.11 (m, 5H), 2.50 (dd, 1H, J=5 and 15Hz), 2.37 (dd, 1H, J=8 and 15Hz), 1.71-1.88 (m, 2H), 1.18 (t, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 3554, 3003, 2983, 2932, 1718, 1600, 1498, 1470, 1301, 1245, 1173. MS (ES) m/e, 239. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found C, 65.32; H, 7.42.

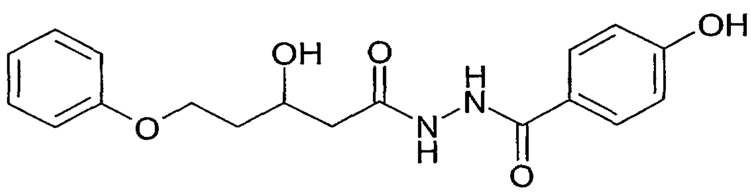
b) 3-hydroxy-5-phenoxypentanoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 8b, from 3-hydroxy-5-phenoxypentanoic acid ethyl ester (6.35 g, 26.6 mmol) and lithium hydroxide 1.91 g, 79.9 mmol) to afford 5.08 g (91%) of 3-hydroxy-5-phenoxypentanoic acid as a white solid.

^{1}H NMR (DMSO-d6) δ 7.24-7.31 (m, 2H), 6.88-6.94 (m, 3H), 3.94-4.09 (m, 3H), 2.41 (dd, 1H, J=5, 15Hz), 2.30 (dd, 1H, J=8, 15Hz), 1.65-1.93 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3516, 3028, 2952, 2932, 2883, 1710, 1600, 1498, 1423, 1244, 1230, 1173. MS (ES) m/e, 211, 209. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found C, 63.03; H, 6.59.

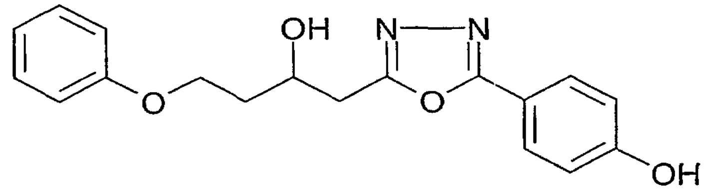
c) 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxypentanoyl)hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 3-hydroxy-5-phenoxypentanoic acid (2.35 g, 8.0 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.97 g, 8.0 mmol) and 4-hydroxybenzoic hydrazide (1.21 g, 8.0 mmol) to afford 2.33 g (85%) of 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxy pentanoyl)hydrazide as a solid.

^{1}H NMR (DMSO-d6) δ 10.07 (bs, 2H), 9.77 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.22-7.31 (m, 2H), 6.89-6.95 (m, 3H), 6.89-6.95 (m, 3H), 6.80 (d, 2H,J=9Hz), 4.84 (d, 1H, J=5Hz), 4.01-4.16 (m, 3H), 2.29-2.43 (m, 2H), 1.89-2.02 (m, 1H), 1.68-1.82 (m, 1H). IR (KBr, cm^{-1}) 3413, 3207, 2949, 2875, 1661, 1601, 1579, 1475, 1469, 1244, 1056, 835. MS (ES) m/e, 345,343. Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85, N, 8.13. Found C, 62.68; H, 5.83; N, 8.26.

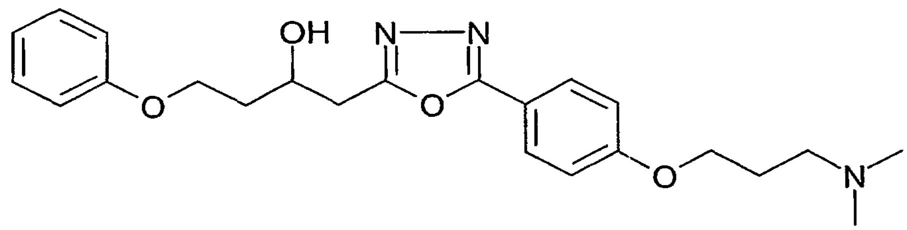
d) 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol



To a heavy suspension of 4-Hydroxybenzoic acid-N-(3-hydroxy-5-phenoxypentanoyl)hydrazide (0.900 g, 2.6 mmol) in 6 mL chlorobenzene stirring at room temperature was added 1,1,3,3-hexamethyldisilazane (1.31 g, 8.1 mmol) followed by trifluoromethane sulfonic acid (0.392 g, 2.6 mmol). The mixture was then heated at 120°C for 6 hours. After cooling to room temperature the suspension was filtered. The filtrate was treated with methanol then concentrated to an oil. The oil was dissolved into EtOAc and washed twice with 5N HCl. The aqueous phases were combined then extracted twice with EtOAc. The organic phases were combined, dried over sodium sulfate, filtered and concentrated to afford an oil. Purification by chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.280g (33%) of 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol as a solid.

^{1}H NMR (DMSO-d6) δ 10.24 (bs, 1H), 7.78-7.82 (m, 2H), 7.24-7.31 (m, 2H), 6.89-6.96 (m, 5H), 5.14 (d, 1H, J=6Hz), 4.02-4.21 (m, 3H), 3.11 (dd, 1H, J=5, 15Hz), 2.99 (dd, 1H, J=8, 15Hz), 1.74-2.05 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3204, 1617, 1599, 1587, 1501, 1473, 1279, 1244, 1173, 844, 754, 739. MS (ES) m/e, 327. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found C, 60.90; H, 4.97; N, 6.95.

e) 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol



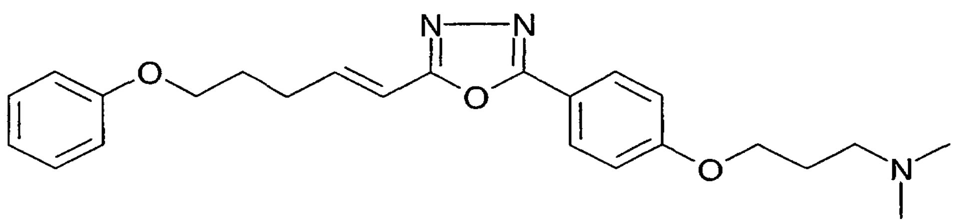
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-[5-(2-Hydroxy-4-phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol (0.260 g 0.8 mmol), sodium hydride (0.064g, 1.6 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.126 g, 0.8 mmol) to afford the title compound as a

crude mixture. Purification by chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:Et_2O) followed by crystallization from MeOH:Et2O afforded 0.129 g (39%) of 1-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}-4-phenoxybutan-2-ol.

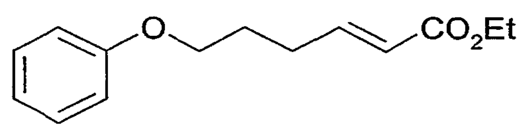
^{1}H NMR (DMSO-d6) δ 7.88-7.91 (m, 2H), 7.24-7.30 (m, 2H), 7.12 (d, 2H, J=9Hz), 6.89-6.95 (m, 3H), 5.15 (d, 1H, J=6Hz), 4.07-4.21 (m, 5H), 3.12 (dd, 1H, J=5,15Hz), 3.00 (dd, 1H, J=8, 15Hz), 2.35 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.77-2.05 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3535, 3019, 2953, 2825, 2777, 1614, 1500, 1470, 1255, 1174. MS (ES) m/e, 412. Anal. Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10, N, 10.21. Found C, 66.98; H, 6.96; N, 10.19. Mp(°C)=93.

Example 21

Preparation of Dimethyl-(3-{4-[5-(5-phenoxypent-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine from 4-Phenoxybutan-1-01



a) 6-Phenoxyhex-2-enoic acid ethyl ester

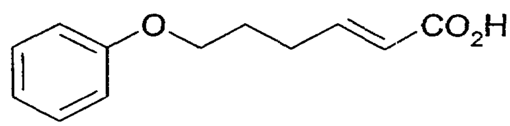


To a solution of oxalyl chloride (5.39 g, 42.5 mmol) in 500 mL CH_2Cl_2 at –78°C was added dimethyl sulfoxide (6.64 g, 85.0 mmol). The reaction was stirred 10 minutes before a solution of 4-Phenoxybutan-1-01 (6.42 g, 38.6 mmol) in 40 mL CH_2Cl_2 was added dropwise over a 25 minute period. The reaction was continued stirring at –78 °C for 30 minutes before triethylamine (19.54 g, 193.1 mmol) was added. The cooling bath was removed allowing the reaction to gradually warm to room temperature. Upon warming, at approximately –40°C (carboethoxymethylene)triphenylphosphorane was added directly followed by 250 mL CH_2Cl_2. The resultant solution was stirred approximately 18 hours at room temperature before being concentrated to an oil. Treatment of the oil with diethyl ether followed by sonication resulted in crystal

formation. Crystals were collected by filtration and discarded. The filtrate was concentrated to an oil and the above process was repeated to remove additional triphenylphosphine oxide. Purification by chromatography on silica gel (elution with 10% Et_2O:hexane) afforded 7.05 g (78%) of *trans*-6-Phenoxyhex-2-enoic acid ethyl ester and 0.520 g (6%) of *cis*-6-Phenoxyhex-2-enoic acid ethyl ester as oils.

^1H NMR (DMSO-d6) δ 7.24-7.31 (m, 2H), 6.89-7.00 (m, 4H), 5.88 (dt, 1H, J=1 and 15Hz), 4.10 (q, 2H, J=7Hz), 3.96 (t, 2H, J=6Hz), 2.36 (ddd, 2H, J=1, 7 and 16Hz), 1.82-1.92 (m, 2H), 1.20 (t, 3H, J=7Hz). IR ($CHCl_3$, cm^{-1}) 1711, 1600, 1498, 1277, 1246, 1172, 1041. MS (ES) m/e, 235. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found C, 71.30; H, 7.73.

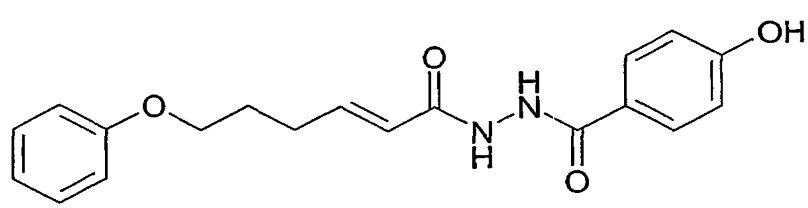
b) *trans*-6-Phenoxyhex-2-enoic acid



A solution of *trans*-6-Phenoxyhex-2-enoic acid ethyl ester (2.25 g, 9.6 mmol) in 48 mL acetone and 48 mL 1N lithium hydroxide was stirred at room temperature for 2.5 hours. The mixture was then quenched with 4.14 mL concentrated HCl, reduced in volume and set aside at 5 °C to allow for crystal formation. Collection of the crystals by filtration afforded 1.43 g (72%) of *trans*-6-phenoxyhex-2-enoic acid.

^1H NMR (DMSO-d6) δ 12.10 (bs, 1H), 7.24-7.31 (m, 2H), 6.83-6.93 (m, 4H), 5.77-5.83 (m, 1H), 3.96 (t, 2H, J=6Hz), 2.30-2.38 (m, 2H), 1.81-1.91 (m, 2H). IR (KBr, cm^{-1}) 3441, 2942, 1693, 1642, 1291, 1252, 1242, 758. MS (ES) m/e, 205. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found C, 70.02; H, 7.06.

c) 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide

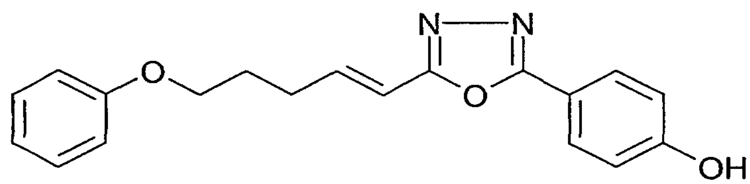


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from *trans*-6-phenoxyhex-2-enoic acid (1.30 g, 6.3 mmol),

2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.56 g, 6.3 mmol) and 4-hydroxybenzoic hydrazide (0.959 g, 6.3 mmol) to afford the title compound as a crude mixture. Purification by crystallization (MeOH:Et_2O) afforded 1.05 g (49%) of 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide.

^{1}H NMR (DMSO-d6) δ 10.09 (bs, 2H), 9.87 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.22-7.32 (m, 2H), 6.89-6.95 (m, 3H), 6.76-6.86 (m, 3H), 6.02-6.07 (m, 1H), 3.99 (t, 2H, J=6Hz), 2.35 (q, 2H, J=7Hz), 1.88 (m, 2H). IR (KBr, cm^{-1}) 3284, 3210, 3007, 1693, 1618, 1610, 1600, 1585, 1518, 1492, 1291, 1245, 1173, 937, 758. MS (ES) m/e, 341, 339. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found C, 66.90; H, 6.03; N, 8.57.

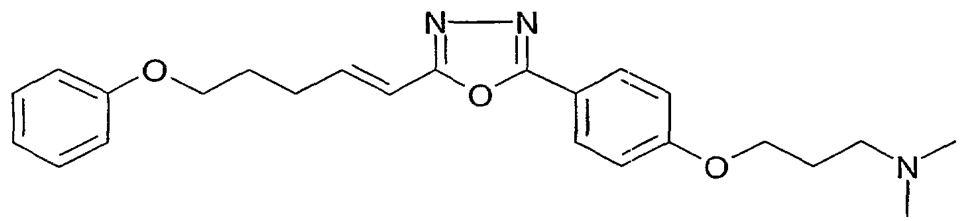
d) 4-[5-(5-phenoxypent-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-Hydroxybenzoic acid-N-(6-phenoxyhex-2-enoyl)hydrazide (0.915 g, 2.7 mmol),triphenylphosphine (1.41 g, 5.4 mmol), triethyl amine (0.544 g, 5.4 mmol) and carbon tetrabromide (1.78 g, 5.4 mmol) to afford the title compound as a crude mixture. Crystallization of this material from EtOAc afforded 0.224 g (26%) of 4-[5-(5-phenoxypent-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.31 (bs, 1H), 7.84-7.89 (m, 2H), 7.25-7.31 (m, 2H), 6.89-6.99 (m, 6H), 6.54-6.59 (m, 1H), 4.03 (t, 2H, J=6Hz), 2.45-2.50 (m, 2H), 1.91-2.00 (m, 2H). IR (KBr, cm^{-1}) 2945, 2612, 1656, 1588, 1441, 1288, 1243, 1173, 1034, 845. MS (ES) m/e, 323, 321. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.64. Found C, 70.70; H, 5.78; N, 8.64.

e) Dimethyl-(3-{4-[5-(5-phenoxypent-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine from 4-Phenoxybutan-1-01

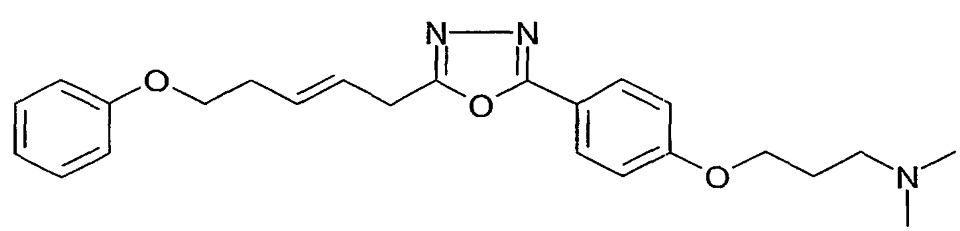


A suspension of 4-[5-(5-phenoxypent-1-enyl)-[1,3,4]oxadiazol-2-yl]phenol (0.207 g 0.6 mmol), cesium carbonate (0.418g, 1.3 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.102 g, 0.6 mmol) in 8.5 mL DMF was heated at 90 °C for 3.5 hours. After cooling to room temperature the reaction was diluted with water then extracted three times with EtOAc. The organic phases were combined, washed with brine then concentrated an oil. Purification by radial chromatography on silica gel (elution with 10% 2M NH3 in MeOH:$CHCl_3$) afforded 0.153 g of the title compound as an oil. Treatment of the oil, dissolved in acetone, with oxalic acid afforded 0.147 g (46%) of the oxalate salt of dimethyl-(3-{4-[5-(5-phenoxypent-1-enyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)amine.

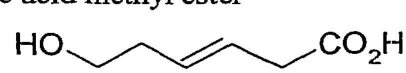
^{1}H NMR (DMSO-d6) δ 7.97 (d, 2H, J=9Hz), 7.23-7.31 (m, 2H), 7.15 (d, 2H, J=9Hz), 6.90-7.03 (m, 4H), 6.56-6.62 (m, 1H), 4.15 (t, 2H, J=6Hz), 4.01-4.05 (m, 2H), 2.76 (s, 6H), 2.04-2.17 (m, 2H), 1.87-1.99 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1776, 1658, 1609, 1493, 1471, 1255, 1172. MS (ES) m/e, 408. Anal. Calcd for $C_{24}H_{29}N_3O_3 \cdot C_2H_2O_4$: C, 62.77; H, 6.28, N, 8.45. Found C, 62.47; H, 6.26; N, 8.32. Mp(°C)=163.

Example 22

Preparation of Dimethyl(3-{4-[5-(5-phenoxypent-2-enyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from Hex-3-enedioic acid monomethyl ester



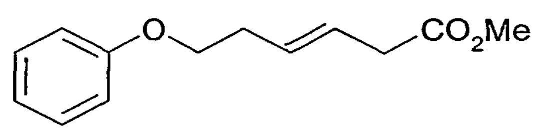
a) 6-Hydroxyhex-3-enoic acid methyl ester



To a solution of hex-3-enedioic acid monomethyl ester (8.49 g, 53.7 mmol) in 23 mL THF at −10 °C was added a 1.0 M solution of borane in THF over a 140 minute period. The resultant suspension was stirred at room temperature approximately 24 hours. Next, the mixture was treated with 1:1 Acetic acid:H_2O then concentrated to an oil. The oil was added dropwise to a 100 mL saturated solution of sodium bicarbonate. This mixture was extracted with EtOAc. The organic phase was washed twice with the saturated solution of sodium bicarbonate. The combined aqueous phases were acidified with 5N HCl then extracted three times with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo to afford 4.09 g (53%) of 6-Hydroxyhex-3-enoic acid methyl ester as an oil.

^{1}H NMR (DMSO-d6) δ 5.45-5.60 (m, 2H), 4.47 (t, 1H, J=5Hz), 3.59 (s, 3H), 3.40 (ddd, 2H, J=5,7,12Hz), 3.04 (d, 2H, J=6Hz), 2.14 (q, 2H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 3620, 3465, 3023, 2955, 2884, 1733, 1438, 1169, 1044, 971. MS (ES) m/e, 126. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found C, 57.43; H, 7.99.

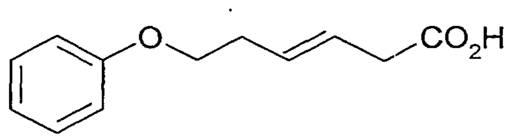
b) 6-Phenxoyhex-3-enoic acid methyl ester



To a solution of 6-hydroxyhex-3-enoic acid methyl (1.30 g, 9.0 mmol) and phenol (1.27 g, 13.5) in 81 mL THF stirring at room temperature was added, in portions, 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide triphenylphosphine adduct (reference: Castro, J. L., Matassa, V. G., *J. Org. Chem.* 1994, *59*, 2289-2291) over a twenty minute period. After stirring approximately 24 hours, the reaction was diluted with EtOAc tehn washed three times with 1N sodium hydroxide, brine, dried over sodium sulfate, filtered, concentrated to a solid. Purification by chromatography on silica gel (elution with 10% Et_2O:hexane) afforded 0.987 g (50%) of 6-phenxoyhex-3-enoic acid methyl ester as an oil.

^{1}H NMR (DMSO-d6) δ 7.24-7.31 (m, 2H), 6.89-6.94 (m, 3H), 5.62-5.65 (m, 2H), 3.97 (t, 2H, J=7Hz), 3.60 (s, 3H), 3.09 (m, 2H), 2.42-2.49 (m, 2H). IR (KBr, cm^{-1}) 3013, 2954, 1734, 1601, 1497, 1438, 1290, 1245, 1173, 1037, 970. MS (ES) m/e, 220. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found C, 56.90; H, 5.84.

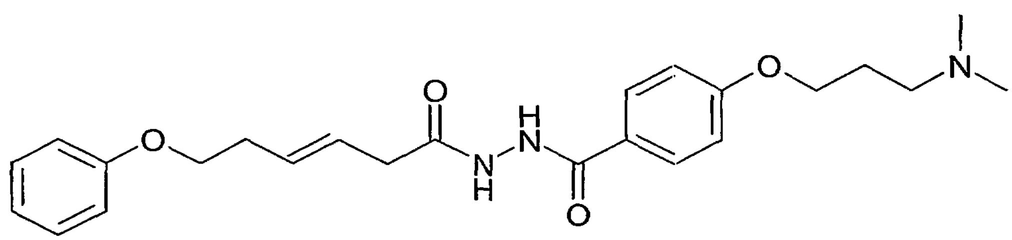
c) 6-Phenxoyhex-3-enoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17c, from 6-phenxoyhex-3-enoic acid methyl ester (0.960 g, 4.4 mmol) and lithium hydroxide (0.313 g, 13.1 mmol) to afford 0.760 g (85%) of 6-phenxoyhex-3-enoic acid as an oil that slowly crystallized out upon standing.

^{1}H NMR (DMSO-d6) δ 12.29 (bs, 1H), 7.20-7.32 (m, 2H), 6.88-6.96(m, 3H), 5.54-5.66 (m, 2H), 3.97 (t, 2H, J=7Hz), 2.99 (m, 2H), 2.43-2.48 (m, 2H). IR (KBr, cm^{-1}) 1713, 1601, 1471, 1398, 1246, 1225, 1039, 968, 758, 694. MS (ES) m/e, 205. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found C, 69.30; H, 6.64.

d) 4-(3-Dimethylaminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide

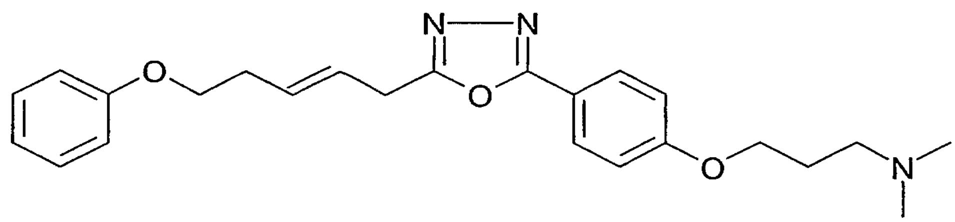


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 6-phenxoyhex-3-enoic acid (0.760 g, 3.7 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.911 g, 3.7 mmol) and 4-(3-dimethylaminopropoxy)benzoic hydrazide (0.874 g, 3.7 mmol) to afford the title compound as an oil. Treatment of the oil with EtOAc followed by 1N HCl resulted in crystal formation in the aqueous phase. The crystals were collected by filtration to afford 0.364 g (23%) of 4-(3-Dimethyl aminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide.

^{1}H NMR (DMSO-d6) δ 10.17 (s, 1H), 9,86 (s, 1H), 7.85 (d, 2H, J=9Hz), 7.24-7.31 (m, 2H), 7.03 (d, 2H, J=9Hz), 6.90-6.95 (m, 3H), 5.57-5.69 (m, 2H), 4.13 (t, 2H, J=6Hz), 3.99 (t, 2H, J=7Hz), 3.17-3.23 (m, 2H), 2.96 (d, 2H, J=3Hz), 2.44-2.48 (m, 2H), 2.11-2.20 (m, 2H). IR (KBr, cm^{-1}) 3201, 3010, 2591, 2563, 2519, 2468, 1683, 1666, 1642, 1609,

1493, 1477, 1467, 1307, 1263, 1166, 978, 762. MS (ES) m/e, 426, 424. Anal. Calcd for $C_{24}H_{31}N_3O_4$: C, 62.40; H, 6.98; N, 9.10. Found C, 61.74; H, 6.83; N, 8.72.

e) Dimethyl(3-{4-[5-(5-phenoxypent-2-enyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

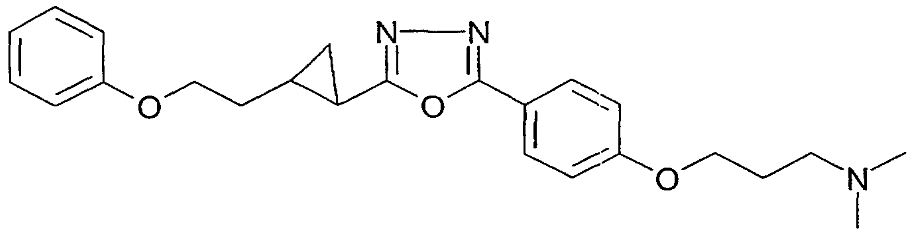


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-Dimethylaminopropoxy)benzoic acid-N-(6-phenoxyhex-3-enoyl)hydrazide (0.348 g, 0.8 mmol),triphenylphosphine (0.217 g, 0.8 mmol), triethyl amine (0.160 g, 1.6 mmol) and carbon tetrabromide (0.275 g, 0.8 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (10% 2M NH_3 in MeOH:$CHCl_3$)afforded 0.224 g of material. The material was dissolved into diethyl ether. To this solution was added dropwise a solution of EtOH in Et2O that was treated with 0.047 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.176 g (53%) of dimethyl(3-{4-[5-(5-phenoxypent-2-enyl)-[1,3,4] oxadiazol-2-yl]-phenoxy}propyl)amine as the hydrochloride salt.

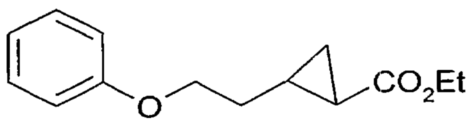
^{1}H NMR (DMSO-d6) δ 7.87-7.93 (m, 2H), 7.23-7.29 (m, 2H), 7.11-7.16 (m, 2H), 6.89-6.94 (m, 3H), 5.78-5.82 (m, 2H), 4.16 (t, 2H, J=6Hz), 4.01 (t, 2H, J=7Hz), 3.71 (d, 2H, J=5Hz), 3.18-3.24 (m, 2H), 2.78 (s, 6H), 2.47-2.53 (m, 2H), 2.13-2.22 (m, 2H). IR (KBr, cm^{-1}) 2936, 2675, 2658, 2614, 2477, 1617, 1501, 1473, 1257, 1175, 972, 839, 769. MS (ES) m/e, 408. Anal. Calcd for $C_{24}H_{29}N_3O_3 \cdot HCl$: C, 64.93; H, 6.81, N, 9.46. Found C, 63.76; H, 6.75; N, 9.24. Analytical HPLC: 100% Purity. Mp(°C)=145.

Example 23

Preparation of Dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenxoy)propyl]amine from 4-phenoxybutene



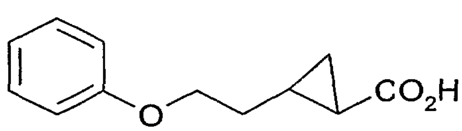
a) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid methyl ester



To a light suspension of 4-phenoxybutene (4.95 g, 33.4 mmol) and rhodium acetate (0.147 g, 0.33 mmol) in 295 mL CH_2Cl_2 stirring at room temperature was added a solution of ethyl diazo acetate (3.81 g, 33.4 mmol) in 48 mL CH_2Cl_2 over a four hour period. Stirring continued for an additional 30 minutes before the mixture was washed twice with 1N HCl, brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with CH_2Cl_2) afforded 1.29 g (16%) of 2-(2-phenoxyethyl)cyclopropanecarboxylic acid methyl ester.

^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 6.90-6.94 (m, 3H),4.12 (m, 2H), 4.02 (ddd, 2H, J=7,9,13Hz), 1.82 (ddd, 1H, J=7,14,21Hz), 1.76 (ddd, 1H, J=6, 13, 21Hz), 1.55 (m, 1H), 1.48 (dd, 1H, J=5,8Hz), 1.26 (t, 3H), 1.22 (ddd, 1H, 4,4,9Hz), 0.79 (ddd, 1H, J=4,6,8Hz). IR ($CHCl_3$, cm^{-1}) 3009, 2984, 2941, 2873, 1717, 1600, 1498, 1302, 1246, 1182, 1039. MS (EI) m/e, 234. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found C, 69.01; H, 7.53.

b) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid

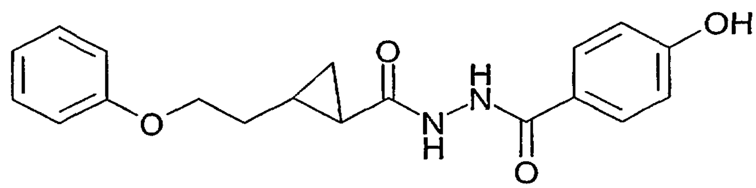


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid methyl ester (1.07 g, 4.5 mmol) and lithium hydroxide (0.33 g, 13.6 mmol) to afford the title compound as a crude mixture. The material was treated with water then extracted twice with EtOAc. The organic phases were combined, dried over sodium sulfate, filtered,

concentrated to afford 0.771 g (82%) 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid as a solid.

^{1}H NMR (DMSO-d6) δ 12.13 (bs, 1H),7.24-7.31 (m, 2H), 6.89-6.95 (m, 3H), 3.94-4.06 (m, 2H), 1.66-1.75 (q, 2H, J=7Hz), 1.31-1.45 (m, 2H), 1.00 (ddd, 1H, J=4,8,17Hz), 0.78 (ddd, 1H, J=4,6,8Hz). IR ($CHCl_3$, cm^{-1}) 3020, 2943, 1696, 1600, 1498, 1246. MS (ES) m/e, 205. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found C, 69.50; H, 6.90.

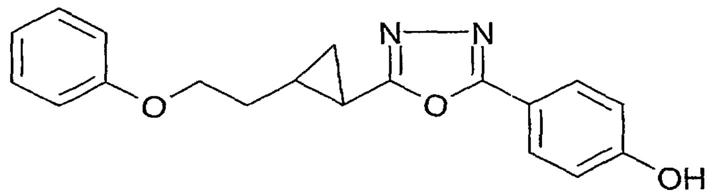
c) 4-Hydroxybenzoic acid-N-[2-(2-phenoxyethyl)cyclopropane carbonyl]hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 2-(2-Phenoxyethyl)cyclopropanecarboxylic acid (0.750 g, 3.6 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.899 g, 3.6 mmol) and 4-hydroxybenzoic hydrazide (0.553 g, 3.6 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% MeOH:$CHCl_3$) followed by crystallization from MeOH:EtOAc afforded 0.336 g (27%) of 4-hydroxybenzoic acid-N-[2-(2- phenoxyethyl)-cyclopropanecarbonyl]hydrazide.

^{1}H NMR (DMSO-d6) δ 10.06-9.97 (M, 3H), 7.80-7.71 (m, 2H), 7.32-7.21 (m, 2H), 6.90-6.96 (m, 3H), 6.79-6.83 (m, 2H),4.02 (t, 2H, J=6Hz), 1.68-1.79 (m, 2H), 1.55-1.61 (m, 1H), 1.28-1.36 (m, 1H), 0.92-0.98 (m, 1H), 0.74-0.80 (m, 1H). IR (KBr, cm^{-1}) 3301, 3226, 1696, 1620, 1610, 1584, 1518, 1498, 1290, 1248, 1173, 756. MS (ES) m/e, 341, 339. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found C, 66.78; H, 5.76; N, 8.26.

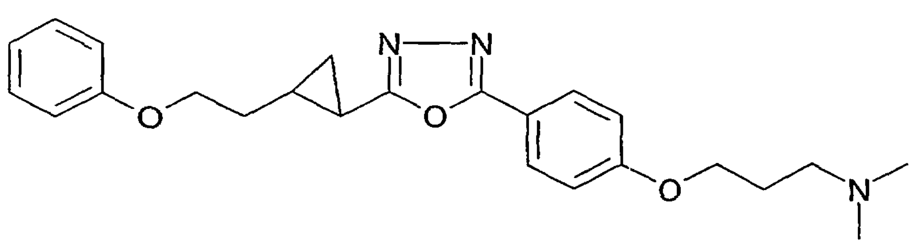
d) 4-{5-[2-(2-Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-N-[2-(2-phenoxyethyl)cyclopropanecarbonyl]hydrazide (0.308 g, 0.9 mmol),triphenylphosphine (0.285 g, 1.1 mmol), triethyl amine (0.110 g, 1.1 mmol) and carbon tetrabromide (0.360 g, 1.1 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with EtOAc) afforded 0.247 mg (85%) of (4-{5-[2-(2- Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol 0.247 g (85%) as a white foam.

^{1}H NMR (DMSO-d6) δ 10.23 (bs, 1H), 7.73-7.81 (m, 2H), 7.24-7.31 (m, 2H), 6.88-6.96 (m, 5H), 4.05-4.12 (m, 2H), 2.16-2.22 (m, 1H), 1.77-1.90 (m, 2H), 1.56-1.64 (m, 1H), 1.26-1.32 (m, 1H), 1.06-1.14 (m, 1H). IR (KBr, cm^{-1}) 3422, 3092, 3027, 2954, 2813, 2684, 2606, 1615, 1601, 1585, 1565, 1500, 1478, 1381, 1287, 1269, 1249, 1175, 1167, 1078, 1032, 1008, 835, 752, 741, 689. MS (ES) m/e, 323, 321. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 69.53; H, 5.51; N, 8.28.

e) Dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenxoy)propyl]amine



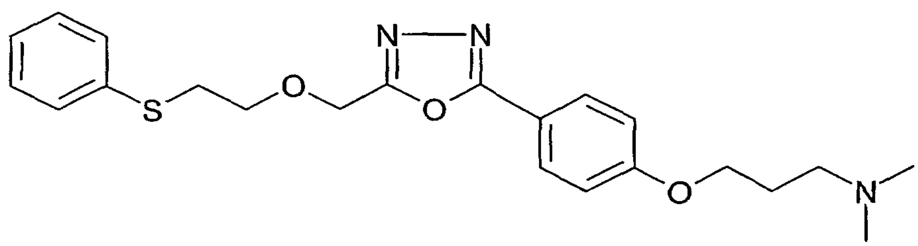
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-{5-[2-(2-Phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenol (0.227 g 0.7 mmol), cesium carbonate (0.459g, 1.4 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.111 g, 0.7 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:Et_2O) afforded an oil. Treatment of the oil, in

acetone, with oxalic acid afforded 0.214 g (61%) of dimethyl-[3(4-{5-[2-(2-phenoxyethyl)cyclopropyl]-[1,3,4]oxadiazol-2-yl}phenxoy)propyl]amine as the oxalate salt.

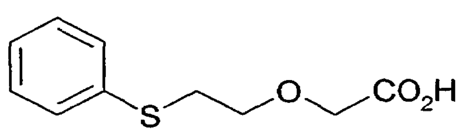
^{1}H NMR (DMSO-d6) δ 7.87 (d, 2H, J=9Hz), 7.24-7.31 (m, 2H), 7.11 (d, 2H, J=9Hz), 6.89-6.96 (m, 3H), 4.05-4.15 (m, 4H), 3.13-3.18 (m, 2H), 2.75 (s, 6H), 2.01-2.20 (m, 3H), 1.78-1.90 (m, 2H), 1.54-1.68 (m, 1H), 1.28-1.34 (m, 1H), 1.15 (ddd, 1H, J=5,6,8Hz). IR ($CHCl_3$, cm^{-1}) 3000, 1777, 1655, 1615, 1501, 1302, 1250, 1224, 1175. MS (ES) m/e, 408. Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 62.77; H, 6.28, N, 8.45. Found C, 62.58; H, 6.28; N, 8.44. Mp(°C)=148.

Example 24

Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-(phenylthio)ethanol



a) (2-Phenylsulfanylethoxy)acetic acid



A suspension of sodium hydride (1.15 g, 28.9 mmol)(washed once with hexane) and 2-(phenylthio)ethanol (4.45 g, 28.9 mmol) in 104 mL DMF was stirred at room temperature for 30 minutes. Next, methyl bromoacetate (4.86 g, 31.7 mmol) was added and the stirring continued for 6.5 hours. The reaction was quenched with water then extracted twice with both hexane followed by EtOAc. The organic phases were combined, washed twice with water, once with brine, dried over sodium sulfate, filtered, concentrated to an oil. The oil was dissolved into 40 mL THF and 20 mL water then treated with lithium hydroxide (2.07 g, 86.6 mmol). The biphasic solution was heated with stirring at 60°C for 1 hour. Upon cooling to room temperature the reaction was quenched with 7.56 mL cocentrated HCl. The reaction was extracted with EtOAc then the

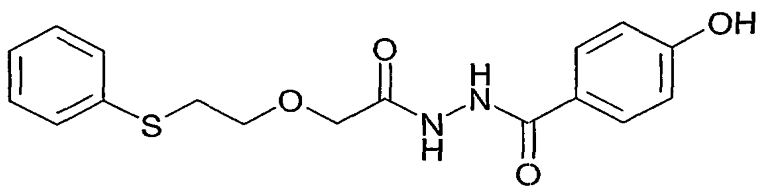
organic phase was washed twice with water, once with brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Purification by chromatography on silica gel (elution with 10% MeOH containing 1% AcOH:CH_2Cl_2) afforded 0.903 g (15%) of (2-phenylsulfanylethoxy)acetic acid.

^{1}H NMR (DMSO-d6) δ 7.29-7.36 (m, 4H), 7.16-7.24 (m, 1H), 3.77 (s, 2H), 3.63 (t, 2H, J=7Hz), 3.14 (t, 2H, J=7Hz).

IR ($CHCl_3$, cm^{-1}) 3051, 1603, 1481, 1440, 1428, 1409, 1116.

MS (ES) m/e, 211. Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found C, 52.81; H, 5.54.

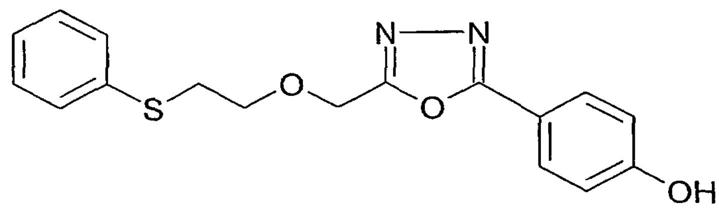
b) 4-Hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy]hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (2-Phenylsulfanylethoxy)acetic acid (0.800 g, 3.8 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.932 g, 3.8 mmol) and 4-hydroxybenzoic hydrazide (0.573 g, 3.8 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 5% MeOH:$CHCl_3$) afforded 0.183 g (14%) of 4-hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy]hydrazide.

^{1}H NMR (DMSO-d6) δ 10.07 (bs, 2H), 9.68 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.30-7.40 (m, 4H), 7.16-7.22 (m, 1H), 6.81 (d, 2H, J=8Hz), 4.04 (s, 2H), 3.71 (t, 2H, J=7Hz), 3.23 (t, 2H, J=7Hz). IR (KBr, cm^{-1}) 3209, 1692, 1640, 1608, 1507, 1439, 1281, 1236, 1173, 1127, 850, 742, 692. MS (ES) m/e, 347, 345. Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found C, 58.52; H, 4.96; N, 8.01.

c) 4-[5-(2-Phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol

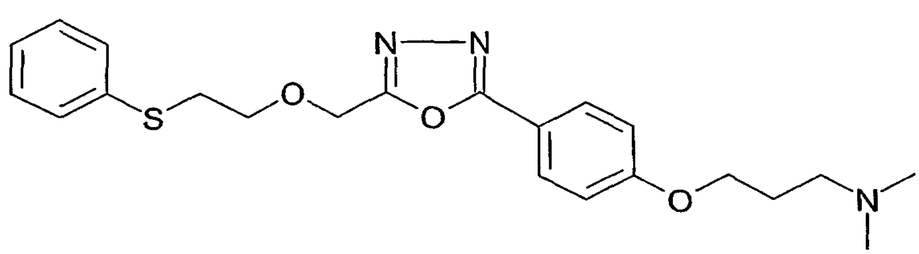


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-Hydroxybenzoic acid N'-[2-(2-phenylsulfanylethoxy]hydrazide (0.161 g, 0.7 mmol), triphenylphosphine (0.244 g, 0.9 mmol), triethyl amine (0.094 g, 0.9 mmol) and carbon tetrabromide (0.308 g, 0.9 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 75% EtOAc:hexane) afforded 0.135 g (88%) of 4-[5-(2-Phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.35 (bs, 1H), 7.82 (d, 2H, J=9Hz), 7.25-7.36 (m, 4H), 7.14-7.20 (m, 1H), 6.95 (d, 2H, J=9Hz), 4.78 (s, 2H), 3.73 (t, 2H, J=7Hz), 3.20 (t, 2H, J=7Hz).

IR (KBr, cm^{-1}) 3586, 3005, 1615, 1603, 1505, 1498, 1482, 1440, 1283, 1171, 1112, 1085, 843. MS (ES) m/e, 329, 327. Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found C, 61.90; H, 4.88; N, 8.35.

d) Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



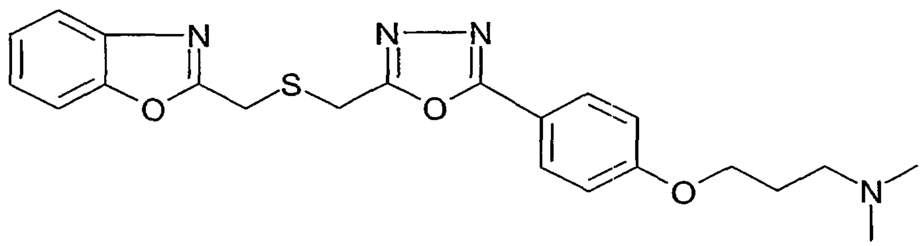
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.114 g 0.4 mmol), cesium carbonate (0.226 g, 0.7 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.055g, 0.4 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:$CHCl_3$) followed by treatment of the isolated material with oxalic acid in

acetone afforded 0.130 g (74%) of Dimethyl-(3-{4-[5-(2-phenylsulfanylethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine as the oxalate salt.

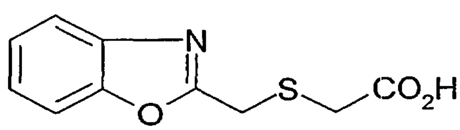
^{1}H NMR (DMSO-d6) δ 7.93 (d, 2H, J=7Hz), 7.25-7.36 (m, 4H), 7.13-7.20 (m, 3H), 4.80 (s, 2H), 4.15 (t, 2H,J=6Hz), 3.74 (t, 2H, J=6Hz), 3.14-3.23 (m, 4H), 2.76 (s, 6H), 2.09-2.18 (m, 2H). IR (KBr, cm^{-1}) 3432, 3037, 2930, 2874, 1726, 1611, 1496, 1258, 1109, 742. MS (ES) m/e, 414. Anal. Calcd for $C_{22}H_{27}N_3O_3S \cdot C_2H_2O_4$: C, 57.24; H, 5.80; N, 8.34. Found C, 57.14; H, 5.71; N, 8.27. Mp(°C)=143.

Example 25

Preparation of (3-{4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadizol-2-yl]phenoxy}propyl)dimethylamine from 2-Chloromethylbenzoxazole



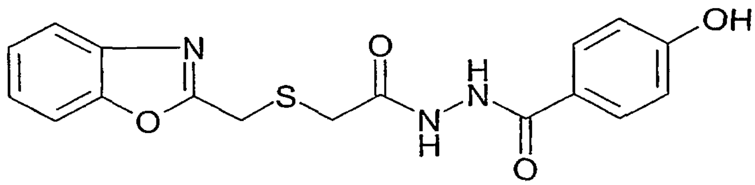
a) (Benzooxazol-2-ylmethylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-Chloromethylbenzoxazole (1.57 g, 9.4 mmol), methylthio-glycolate (0.994 g, 9.4 mmol), and sodium hydride (0.375 g, 9.4 mmol) to afford the title compound as a crude mixture. Purification by crystallization with Et2O afforded 1.12 g (54%) of (Benzo-oxazol-2-ylmethylsulfanyl)acetic acid.

^{1}H NMR (DMSO-d6) δ 12.71 (bs, 1H), 7.68-7.75 (m, 2H), 7.34-7.43 (m, 2H), 4.14 (s, 2H), 3.45 (s, 2H). IR (KBr, cm^{-1}) 2933, 2542, 1725, 1606, 1571, 1454, 1236, 1191, 1133, 840, 767. MS (ES) m/e, 224. Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found C, 53.53; H, 4.02; N, 6.17.

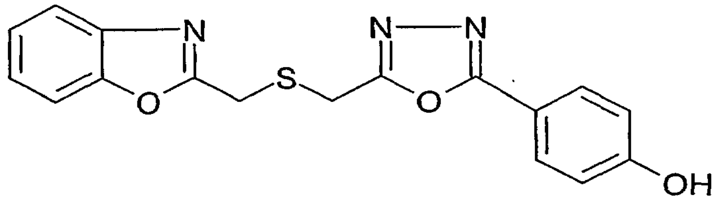
b) 4-Hydroxybenzoic acid-*N'*-[2-benzooxazol-2-ylmethylsulfanyl)acetyl]hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (benzooxazol-2-ylmethylsulfanyl)acetic acid (0.822 g, 3.7 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.911 g, 3.7 mmol) and 4-hydroxybenzoic hydrazide (0.560 g, 3.7 mmol) to afford the title compound as a crude material. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 10% 2M NH_3 in MeOH:$CHCl_3$) afforded 0.190 g (14%) of 4-hydroxy benzoic acid-*N'*-[2-benzooxazol-2-ylmethylsulfanyl)acetyl] hydrazide as a white foam.

^{1}H NMR (DMSO-d6) δ 10.27 (bs, 1H), 9.83 (bs, 1H), 9.38 (bs, 1H), 7.71-7.86 (m, 3H), 6.68-6.94 (m, 5H), 4.20 (s, 2H), 3.61 (s, 2H). IR (KBr, cm^{-1}) 3208, 1658, 1612, 1598, 1497, 1456, 1368, 1282, 1239, 1172, 843, 752. MS (ES) m/e, 358, 356. Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found C, 56.82; H, 4.08; N, 11.71.

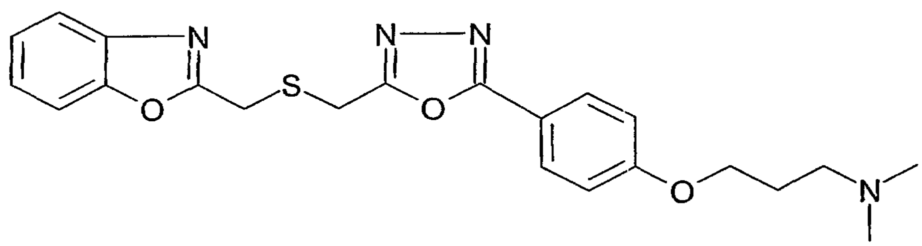
c) 4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-benzooxazol-2-ylmethylsulfanyl)acetyl]hydrazide (0.190 g, 0.5 mmol),triphenylphosphine (0.279 g, 1.1 mmol), triethyl amine (0.108 g, 1.1 mmol) and carbon tetrabromide (0.353 g, 1.1 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) afforded 0.150 g of 4-[5-(Benzooxazol-2-ylmethyl sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenol along with triphenylphosphine as a contaminant.

^{1}H NMR (DMSO-d6) δ 10.29 (bs, 1H), 7.52 (m, 4H), 7.30-7.39 (m, 2H), 6.88-6.93 (m, 2H), 4.24 (d, 4H). IR (KBr, cm^{-1}) 3227, 1609, 1561, 1497, 1452. MS (ES) m/e, 340, 338. Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found C, 63.51; H, 4.23; N, 9.32.

d) (3-{4-[5-(Benzooxazol-2-ylmethylsulfanyl methyl)-[1,3,4]oxadizol-2-yl]phenoxy}propyl)dimethylamine

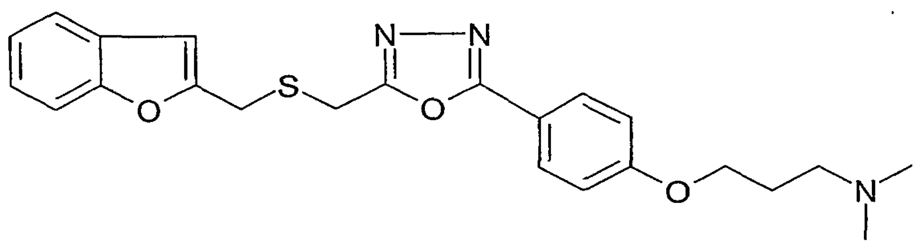


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.131 g, 0.4 mmol), cesium carbonate (0.252 g, 0.8 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.061g, 0.4 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:$CHCl_3$) followed by treatment of the isolated material with oxalic acid in acetone afforded 0.026 g (13%) of (3-{4-[5-(Benzooxazol-2-ylmethylsulfanylmethyl)-[1,3,4]oxadizol-2-yl]phenoxy}propyl)dimethylamine as the oxalate salt.

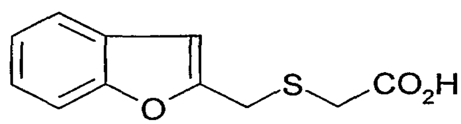
^{1}H NMR (DMSO-d6) δ 7.81 (d, 2H, J=9Hz), 7.60-7.64 (m, 2H), 7.29-7.38 (m, 2H), 7.10 (d, 2H, J=9Hz), 4.25 (d, 4H), 4.14 (t, 2H, J=6Hz), 3.15-3.20 (m, 2H), 2.77 (s, 6H), 2.08-2.17 (m, 2H). IR (KBr, cm^{-1}) 3007, 1777, 1656, 1614, 1500, 1455, 1302, 1254, 1176, 839. MS (ES) m/e, 425. Anal. Calcd for $C_{22}H_{24}N_4O_3S \cdot C_2H_2O_4$: C, 56.02; H, 5.09; N, 10.89. Found C, 55.28; H, 4.84; N, 10.74. Mp(°C)=120.

Example 26

Preparation of (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine from 2-Bromomethylbenzofuran

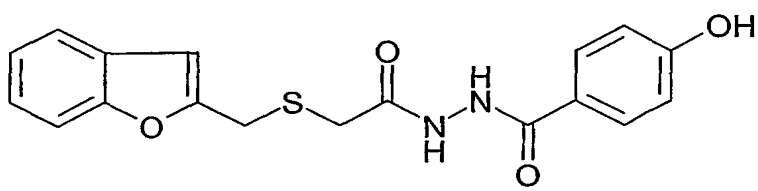


a) (Benzofuran-2-ylmethylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-Bromomethylbenzofuran (3.34 g, 15.8 mmol), methylthioglycolate (2.02 g, 19.0 mmol), and sodium hydride (0.760 g, 19.0 mmol) to afford the title compound as a crude material. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 10% MeOH:CHCl3) afforded 1.46 g of (Benzofuran-2-ylmethylsulfanyl)acetic acid along with other coeluting impurities. Material was taken on to next step without further purification.

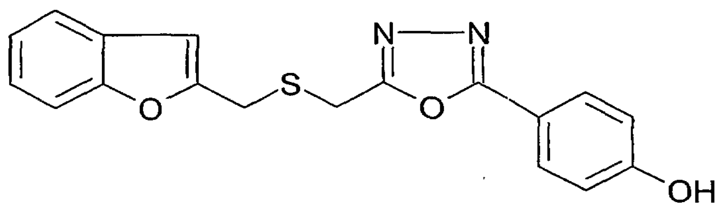
b) 4-Hydroxybenzoic acid-*N'*-[2-benzofuran-2-ylmethylsulfanyl)acetyl]hydrazide



To a solution of benzofuran-2-ylmethylsulfanyl)acetic acid (1.46 g, 6.6 mmol) in 100 mL THF stirring at room temperature was added 1,1'-carbonyldiimidazole (1.07 g, 6.6 mmol). The reaction was heated at 60 $^{\square}$C for one hour. After cooling to room temperature, the mixture was treated with and 4-hydroxybenzoic hydrazide (1.50 g, 9.9 mmol). After stirring for approximately 4 hours the reaction was concentrated to a solid material. The material was partitioned between EtOAc and 1N HCl. The phases were separated and the organic phase was washed twice with 1N HCl, brine, dried over sodium sulfate, filtered, concentrated to afford an oil. Treatment of the oil with CHCl3 followed by sonication afforded 0.854 g (36%) of 4-Hydroxybenzoic acid-*N'*-[2-benzofuran-2-ylmethylsulfanyl)acetyl]hydrazide as a filterable solid.

[1]H NMR (DMSO-d6) δ 10.02 (bs, 1H), 7.76 (d, 2H, J=8Hz), 7.53-7.61 (m, 2H), 7.20-7.31 (m, 2H), 6.83 (m, 3H), 4.09 (s, 2H), 3.27 (s, 2H). IR (KBr, cm^{-1}) 3296, 3211, 3007, 1687, 1625, 1584, 1515, 1452, 1281, 1173, 956, 745. MS (ES) m/e, 357, 355. Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found C, 58.53; H, 4.43; N, 7.93.

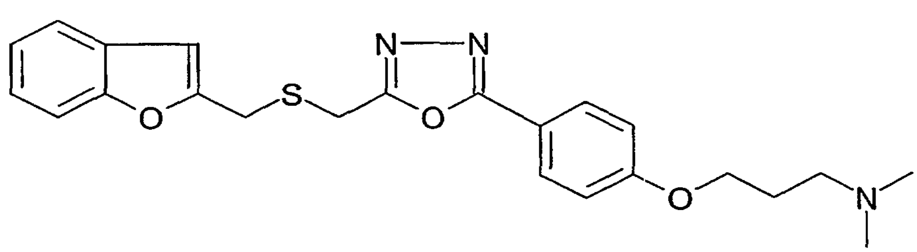
c) 4-[5-(benzofuran-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-benzofuran-2-ylmethylsulfanyl)acetyl]hydrazide (0.753 g, 2.1 mmol),triphenylphosphine (0.665g, 2.5 mmol), triethyl amine (0.256 g, 2.5 mmol) and carbon tetrabromide (0.841 g, 2.5 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 75% EtOAc:hexane) afforded 0.550 g (77%) of 4-[5-(benzofuran-2-ylmethyl sulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol as an oil that slowly crystallized out.

[1]H NMR (DMSO-d6) δ 10.29 (s, 1H), 7.72 (d, 2H, J=8Hz), 7.46-7.57 (m, 2H), 7.17-7.28 (m, 2H), 6.79 (s, 1H), 6.79 (s, 1H), 4.10 (s, 2H), 4.08 (s, 2H). IR (KBr, cm^{-1}) 3429, 3053, 2936, 1611, 1595, 1575, 1452, 1293, 1176, 1097, 953, 844, 757. MS (ES) m/e, 339, 337. Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. Found C, 63.05; H, 4.34; N, 7.26.

d) (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine

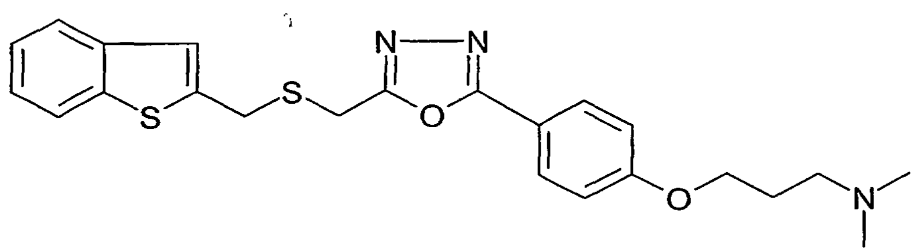


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(benzofuran-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol (0.510 g, 1.5 mmol), cesium carbonate (0.982 g, 3.0 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.238g, 1.5 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:$CHCl_3$) followed by treatment of the isolated material with oxalic acid in acetone afforded 0.364 g (47%) of (3-{4-[5-Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the oxalate salt.

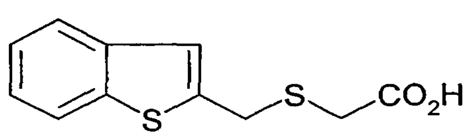
^{1}H NMR (DMSO-d6) δ 7.83 (d, 2H, J=9Hz), 7.45-7.56 (m, 2H), 7.17-7.27 (m, 2H), 7.10 (d, 2H, J=9Hz), 6.79 (s, 1H), 4.09-4.16 (m, 6H), 3.15-3.20 (m, 2H), 2.77 (s, 6H), 2.09-2.18 (m, 2H). IR (KBr, cm^{-1}) 1615, 1500, 1255, 1175, 949, 754, 707. MS (ES) m/e, 424. Anal. Calcd for $C_{23}H_{25}N_3O_3S \cdot C_2H_2O_4$: C, 58.47; H, 5.30; N, 8.18. Found C, 58.08; H, 5.22; N, 8.08. Mp(°C)=144.

Example 27

Preparation of (3-{4-[5-Benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine from 2-bromomethylbenzo[*b*]thiophene



a) (Benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid

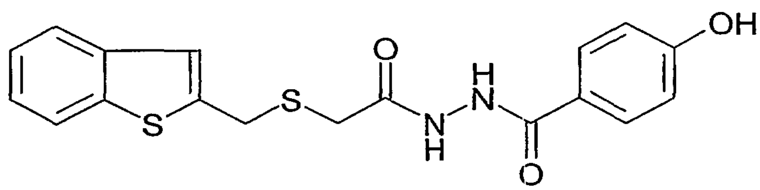


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-bromomethylbenzo[*b*]thiophene (2.21 g, 9.7 mmol), methylthioglycolate (1.03 g, 9.7 mmol), and sodium hydride (0.389 g, 9.7 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 2 to 10% MeOH:CHCl3) followed by crystallization of the isolated

material from Et_2O:hexane afforded 1.16 g (50%) of (benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid.

^1H NMR (DMSO-d6) δ 12.65 (bs, 1H), 7.89-7.92 (m, 1H), 7.76-7.80 (m, 1H), 7.29-7.38 (m, 3H), 4.16 (s, 2H), 3.24 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3010, 2917, 2673, 2568, 1710, 1458, 1436, 1297, 1132. MS (ES) m/e, 237. Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.44; H, 4.23. Found C, 55.41; H, 4.13.

b) 4-Hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl)acetyl]hydrazide

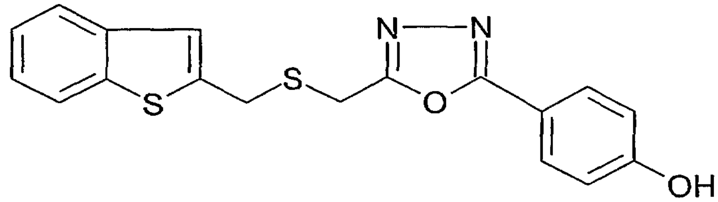


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (benzo[*b*]thiophene-2-ylmethylsulfanyl)acetic acid (1.00 g, 4.2 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.04 g, 4.2 mmol) and 4-hydroxybenzoic hydrazide (0.638 g, 4.2 mmol) to afford the title compound. The resultant crystals that had formed upon concentration of the crude material were collected by filtration to afford 0.982 g (63%) of 4-Hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl)acetyl]hydrazide.

^1H NMR (DMSO-d6) δ 10.17 (bs, 1H), 10.09 (bs, 1H), 9.99 (bs, 1H), 7.89-7.93 (m, 1H), 7.75-7.79 (m, 3H), 7.22-7.38 (m, 3H), 6.82 (d, 2H, J=9Hz), 4.24 (s, 2H), 3.24 (s, 2H).

IR (KBr, cm^{-1}) 3311, 3200, 3004, 1685, 1624, 1610, 1585, 1547, 1518, 1495, 1331, 1285, 1234, 1175, 1109, 747. MS (ES) m/e, 373. Anal. Calcd for $C_{18}H_{18}N_2O_3S_2$: C, 57.73; H, 4.84; N, 7.48. Found C, 57.95; H, 4.09; N, 7.29.

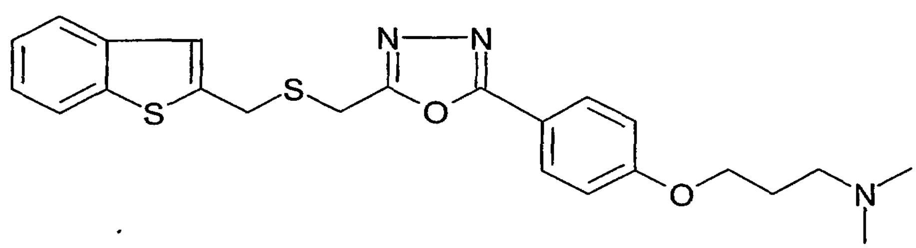
c) 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-benzo[*b*]thiophen-2-ylmethylsulfanyl)acetyl]hydrazide (0.611 g, 1.6 mmol),triphenylphosphine (0.860g, 3.3 mmol), triethyl amine (0.332 g, 3.3 mmol) and carbon tetrabromide (1.09 g, 3.3 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 50% EtOAc:hexane) followed by the filtration of the resultant crystals in the eluent afforded 0.208 g (36%) of 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.29 (s, 1H), 7.87-7.90 (m, 1H), 7.72-7.78 (m, 3H), 7.28-7.37 (m, 3H), 6.92 (d, 2H, J=9Hz), 4.22 (s, 2H), 4.04 (s, 2H). IR (KBr, cm^{-1}) 3160, 2982, 2932, 1609, 1599, 1565, 1498, 1457, 1282, 1221, 1175, 742. MS (ES) m/e, 355. Anal. Calcd for $C_{18}H_{16}N_2O_3S_2$: C, 60.65; H, 4.52; N, 7.86. Found C, 61.72; H, 4.26; N, 7.31.

d) (3-{4-[5-Benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



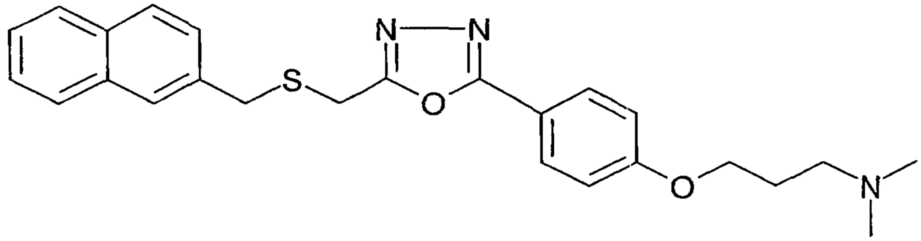
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(benzo[*b*]thiophene-2-ylmethylsulfanylmethyl) [1,3,4]oxadiazol-2-yl]phenol (0.178 g, 0.5 mmol), cesium carbonate (0.325 g, 1.0 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.079g, 0.5 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:$CHCl_3$) followed by crystallization of the isolated

material from Et2O afforded 0.115 g (52%) of (3-{4-[5-benzo[*b*]thiophene-2-ylmethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)dimethylamine.

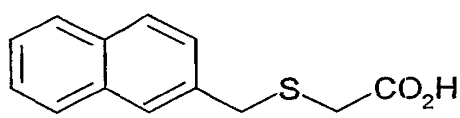
^{1}H NMR (DMSO-d6) δ 7.74-7.89 (m, 4H), 7.27-7.36 (m, 3H), 7.08 (d, 2H, J=9Hz), 4.23 (s, 2H), 4.05-4.11 (m, 4H), 2.36 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.88 (m, 2H). IR (KBr, cm^{-1}) 3432, 2940, 2814, 2761, 1587, 1616, 1563, 1500, 1469, 1428, 1305, 1256, 1177, 1153, 1088, 1051, 821, 740, 728. MS (ES) m/e, 438. Anal. Calcd for $C_{23}H_{25}N_3O_3S_2$: C, 62.15; H, 5.62; N, 9.24. Found C, 62.84; H, 5.73; N, 9.56. Mp(°C)=93.

Example 28

Preparation of Dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-Bromomethylnaphthalene



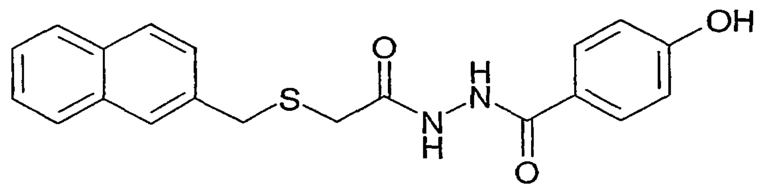
a) (Naphthalen-2ylmethylsulfanyl)acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 2-bromomethylnaphthalene (1.86 g, 8.4 mmol), methylthioglycolate (0.982 g, 9.3 mmol), and sodium hydride (0.370 g, 9.3 mmol) to afford the title compound as a crude mixture. Crystallization from Et_2O afforded 1.01 g (52%) of (Naphthalen-2ylmethylsulfanyl)acetic acid.

^{1}H NMR (DMSO-d6) δ 12.60 (bs, 1H), 7.86-7.91 (m, 3H), 7.78 (s, 1H), 7.46-7.54 (m, 3H), 3.98 (s, 2H), 3.13 (s, 2H).
IR ($CHCl_3$, cm^{-1}) 3059, 3019, 3010, 1709, 1601, 1510, 1422, 1295, 1230, 1126, 820. MS (ES) m/e, 231. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found C, 73.11; H, 4.83.

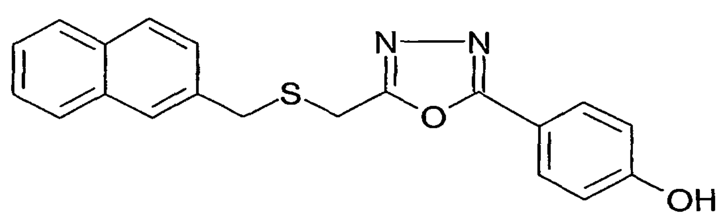
b) 4-Hydroxybenzoic acid-*N'*-[2-(naphthalen2-ylmethylsulfanyl)acetyl]hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (Naphthalen-2-ylmethylsulfanyl)acetic acid (1.00 g, 4.3 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.06 g, 4.3 mmol) and 4-hydroxybenzoic hydrazide (0.655 g, 4.3 mmol) to afford the title compound. The resultant crystals that had formed upon concentration of the crude material were collected by filtration to afford 0.761 g (48%) of 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-2-ylmethylsulfanyl) acetyl]hydrazide

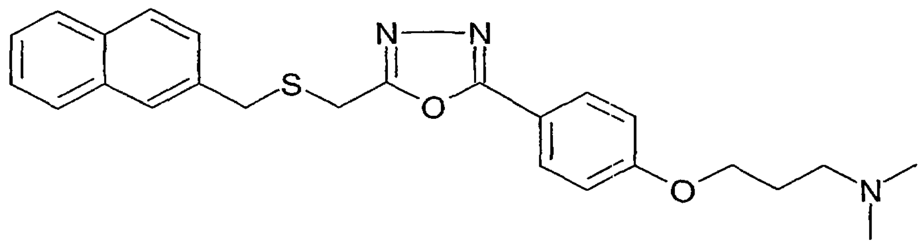
^{1}H NMR (DMSO-d6) δ 10.18 (bs, 1H), 10.09 (bs, 1H), 9.99 (bs, 1H), 7.83-7.97 (m, 4H), 7.77 (d, 2H,J=9Hz), 7.45-7.55 (m, 3H), 6.83 (d, 2H, J=9Hz), 4.06 (s, 2H), 3.15 (s, 2H). IR (KBr, cm^{-1}) 3206, 3055, 3005, 1688, 1622, 1610, 1584, 1549, 1517, 1495, 1289, 1234, 1173, 750. MS (ES) m/e, 367, 365. Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.56; H, 4.95; N, 7.64. Found C, 65.74; H, 4.69; N, 7.58.

c) 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-2-ylmethylsulfanyl)acetyl]hydrazide (0.562 g, 1.5 mmol),triphenylphosphine (0.805g, 3.1 mmol), triethyl amine (0.310 g, 3.1 mmol) and carbon tetrabromide (1.02 g, 3.1 mmol) to afford the title compound as a crude mixture. Attempts to purify material by silica gel radial chromatogrpahy failed. Material taken on to next step without further purification.

d) Dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



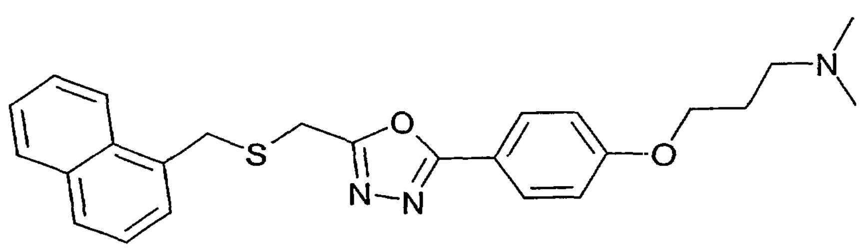
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.534 g, 1.5 mmol), cesium carbonate (0.999 g, 3.1 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.242g, 1.5 mmol) to afford the title compound. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:$CHCl_3$)afforded 0.155 g of the title compound as a solid. This material was dissolved into Et2O then treated with a solution of EtOH that was treated with acetyl chloride (0.030 mL, 0.43 mmol). The resultant precipitate was collected by filtration to afford 0.103 g (16%) of dimethyl-(3-{4-[5(naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine as the hydrochloride salt.

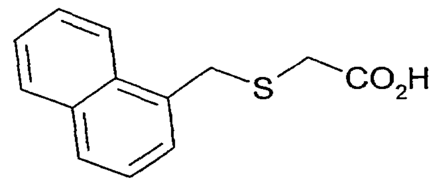
^{1}H NMR (DMSO-d6) δ 7.89-7.82 (m, 6H), 7.46-7.53 (m, 3H), 7.11 (d, 2H, J=9Hz), 4.16 (t, 2H, J=6Hz), 4.05 9s, 2H), 3.99 (s, 2H), 3.21 (m, 2H), 2.78 (s, 6H), 2.13-2.22 (m, 2H).

IR (KBr, cm^{-1}) 3428, 3015, 2956, 2605, 2482, 1613, 1567, 1498, 1486, 1473, 1473, 1428, 1392, 1309, 1260, 1243, 1182, 1088, 1055, 941, 832, 752, 734. MS (ES) m/e, 434. Anal. Calcd for $C_{25}H_{27}N_3O_2S{\cdot}HCl$: C, 63.88; H, 6.00; N, 8.94. Found C, 63.05; H, 5.88; N, 8.65. Analytical HPLC: 100% Purity. Mp(°C)=194.

Example 29

Preparation of Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 1-bromomethylnaphthalene.



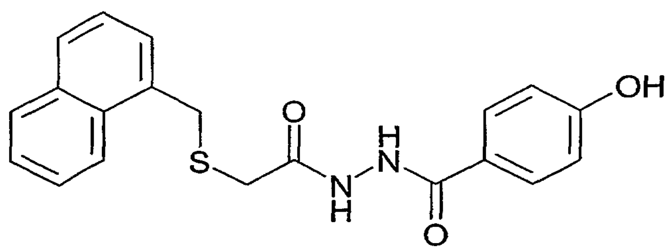


a) (Naphthalen-2ylmethylsulfanyl)acetic acid

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 17b, from 1-bromomethylnaphthalene (10.71 g, 48.4 mmol), methylthio glycolate (3.57 g, 38.3 mmol), and sodium hydride (3.10 g, 77.5 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 3 x 500 mL CH_2Cl_2, 3 x 500 mL 10% MeOH:CH_2Cl_2) afforded 6.76 g (75%) of(naphthalen-1yl- methylsulfanyl)acetic acid.

^{1}H NMR (DMSO-d6) δ 12.68 (bs, 1H), 8.16-8.20 (m, 1H), 7.90-7.97 (m, 1H), 7.83-7.88 (m, 1H), 7.50-7.60 (m, 2H), 7.41-7.48 (m, 2H), 4.30 (s, 2H), 3.20 (s, 2H). IR (KBr, cm^{-1}) 3065, 3050, 3001, 2928, 1709, 1597, 1512, 1426, 1399, 1295, 802. MS (EI) m/e, 232

b) 4-Hydroxybenzoic acid-*N'*-[2-(naphthalen2-ylmethylsulfanyl)acetyl]hydrazide

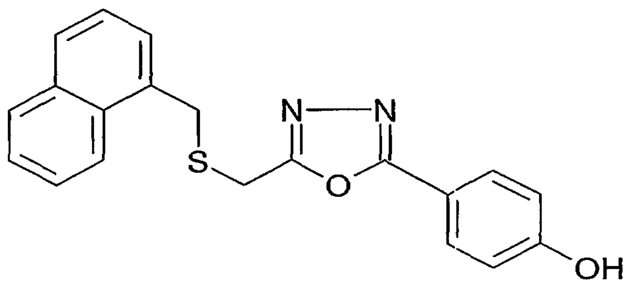


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (Naphthalen-1ylmethylsulfanyl)acetic acid (1.77 g, 7.6 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.89 g, 7.6 mmol) and 4-hydroxybenzoic hydrazide (1.16 g, 7.6 mmol) to afford the title compound as a crude mixture. Crystallization from MeOH:Et2O afforded 1.57 g (56%) of 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-1-ylmethylsulfanyl) acetyl]hydrazide.

^{1}H NMR (DMSO-d6) δ 10.24-10.04 (m, 3H), 8.22 (d, 1H, J=8Hz), 7.94 (d, 1H, J=8Hz), 7.85 (d, 1H, J=8Hz), 7.78 (d, 2H, J=9Hz), 7.43-7.61 (m, 4H), 6.83 (d, 2H, J=9Hz), 4.40 (s, 2H), 3.22 (s, 2H). IR (KBr, cm^{-1}) 3364, 3173, 3017, 1693, 1654, 1610,

1571, 1511, 1495, 1294, 1285, 1237, 1175, 778. MS (ES) m/e, 367, 365. Anal. Calcd for $C_{20}H_{18}N_3O_3S$: C, 65.56; H, 4.95; N, 7.64. Found C, 63.99; H, 4.74; N, 7.33.

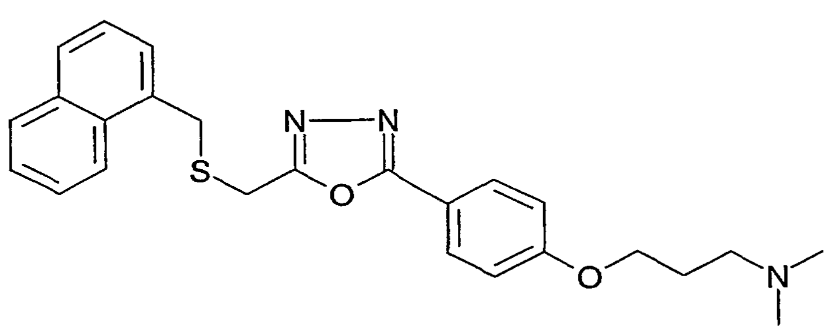
c) 4-[5-(Naphthalen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, using 4-hydroxybenzoic acid-*N'*-[2-(naphthalen-1-ylmethylsulfanyl)acetyl]hydrazide (0.898 g, 2.5 mmol),triphenylphosphine (1.93g, 7.4 mmol), triethyl amine (0.744 g, 7.4 mmol) and carbon tetrabromide (2.44 g, 7.4 mmol) to afford the title compound. Purification by silica gel flash filtration (elution with 50% Et_2O:hexane followed by Et_2O) afforded 0.420 g (49%) of 4-[5-(Naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol as a white solid.

^{1}H NMR (DMSO-d6) δ 10.31 9s, 1H), 8.13-8.17 (m, 1H), 7.91-7.95 (m, 1H), 7.84 (d, 1H, J=8Hz), 7.77 (d, 2H, J=8Hz), 7.38-7.57 (m, 4H), 6.94 (d, 2H, J=8Hz), 4.35 (s, 2H), 4.01 (s, 2H). IR (KBr, cm^{-1}) 3057, 1613, 1594, 1577, 1446, 1293, 1177, 773. MS (ES) m/e, 349, 347. Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04. Found C, 67.72; H, 4.54; N, 7.74.

d) Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

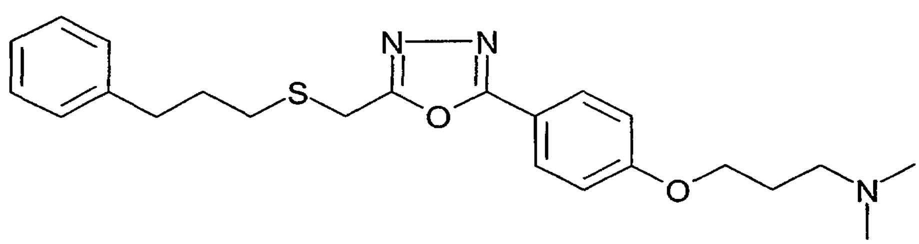


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(Naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.400 g, 1.1 mmol), cesium carbonate (0.748 g, 2.3 mmol) and 3-chloro-N,N-dimethylpropyl amine hydrochloride (0.181g, 1.1 mmol) to afford the title compound. Purification by silica gel radial chromatography (elution with 5% 2M NH_3 in $MeOH:CHCl_3$) afforded 0.374 g of the title compound as a solid. Crystallization from Et2O afforded 0.374 g (75%) of Dimethyl-(3-{4-[5(naphthalen-1-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine.

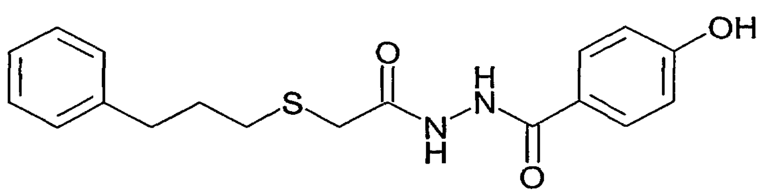
^{1}H NMR (DMSO-d6) δ 8.16—8.13 (m, 1H), 7.92-7.95 (m, 1H), 7.84-7.88 (m, 3H), 7.41-7.57 (m, 4H), 7.12 (d, 2H, J=9Hz), 4.36 (s, 2H), 4.10 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.84-1.93 (m, 2H). IR (KBr, cm^{-1}) 1614, 1500, 1469, 1257, 1175, 839. MS (ES) m/e, 434. Anal. Calcd for $C_{25}H_{27}N_3O_2S$: C, 69.26; H, 6.28; N, 9.69. Found C, 68.35; H, 6.16; N, 9.59. Mp(°C)=96.

Example 30

Preparation of Dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 3-Phenylpropyl mercaptan.



a) 4-Hydroxybenzoic acid *N*'-[2(3-phenylpropylsulfanyl) acetyl]hydrazide



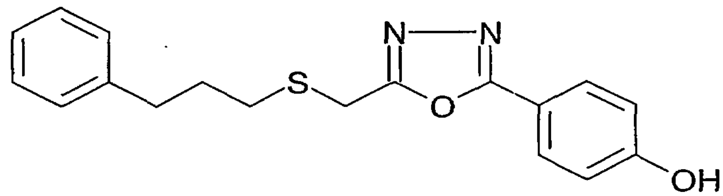
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (3-phenyl propylsulfanyl)acetic acid (2.00 g, 9.5 mmol), 4-hydroxy benzoic hydrazide (1.45 g, 9.5 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.35 g, 9.5 mmol) to afford the title compound as a crude mixture.

Crystallization from methanol and diethyl ether afforded 2.15g (66%) of 4-hydroxybenzoic acid *N'*-[2(3-phenyl propyl sulfanyl) acetyl]hydrazide.

^{1}H NMR (DMSO-d6) δ 10.02-10.13 (m, 2H), 9.94-9.97 (bs, 1H), 7.74 (d, 2H, J=8Hz), 7.14-7.31 (m, 5H), 6.81 (d, 2H, J=9Hz), 3.21 (s, 2H), 2.63-2.69 (m, 4H), 1.80-1.92 (m, 2H).

IR (KBr, cm^{-1}) 3311, 3208, 2859, 1695, 1625, 1609, 1585, 1517, 1495, 1284, 1175, 1115, 848, 694, 567. MS (ES) m/e, 345, 343. Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found C, 62.37; H, 5.86; N, 8.03.

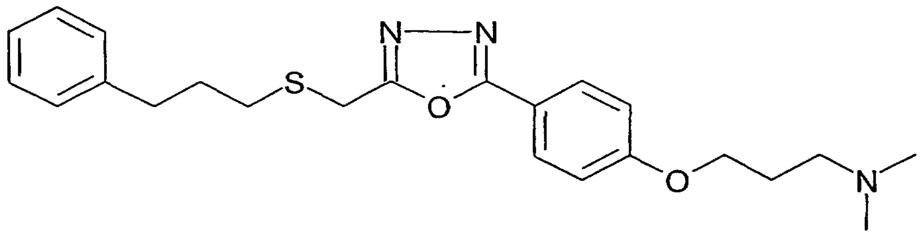
b) 4-[5(3-Phenylpropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-[2(3-phenylpropyl sulfanyl)acetyl] hydrazide (1.94 g, 5.6 mmol), triphenyl phosphine (2.95 g, 11.3 mmol), triethylamine (2.05 g, 20.2 mmol) and carbon tetrabromide (3.55 g, 23.1 mmol) to afford the title compound as a crude material. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from EtOH afforded 0.973 g (53%) of 4-[5(3-phenylpropyl sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.31 (s, 1H), 7.78 (d, 2H, J=9Hz), 7.14-7.27 (m, 5Hz), 6.94 (d, 2H, J=9Hz), 4.07 (s, 2H), 2.60-2.67 (m, 4H), 1.79-1.89 (m, 2H). IR (KBr, cm^{-1}) 3143, 3024, 2938, 1611, 1601, 1499, 1232. MS (ES) m/e, 327, 325. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found C, 65.87; H, 5.47; N, 8.44.

c) Dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

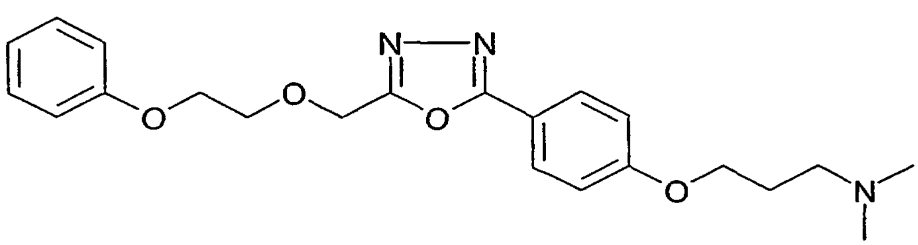


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5(3-phenylpropyl sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.800 g, 2.5 mmol), sodium hydride (0.225 g, 5.6 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.426 g, 2.7 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 IN MeOH:$CHCl_3$) afforded 0.602 g of an oil. The oil was dissolved in diethyl ether. To this solution was added dropwise, a soluiton of EtOH in Et2O that was treated with 0.116 mL acetyl chloride. The resultant precipitate was collected by filtration to afford 0.533 g (50%) of dimethyl-(3-{4-[5-(3-phenylpropylsulfanyl methyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine as the hydrochloride salt.

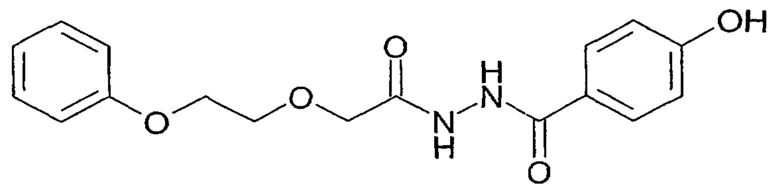
^{1}H NMR (DMSO-d6) δ 7.90 (d, 2H, J=9JHz), 7.22-7.27 (m, 2H), 7.13-7.18 (m, 5H), 4.17 (t, 2H, J=6Hz), 4.09 (s, 2H), 3.19-3.21 (m, 2H), 2.78 (s, 6H), 2.60-2.67 (m, 4H), 2.13-2.22 (m, 2H), 1.79-1.89 (m, 2H). IR ($CHCl_3$, cm^{-1}) 2970, 2337, 1615, 1570, 1500, 1474, 1254, 1176. MS (ES) m/e, 412. Anal. Calcd for $C_{23}H_{29}N_3O_2S{\cdot}HCl$: C, 61.66; H, 6.75; N, 9.38. Found C, 61.30; H, 6.76; N, 9.13. Mp(°C)=148.

Example 31

Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine from 2-(Phenoxyethoxy)acetic acid



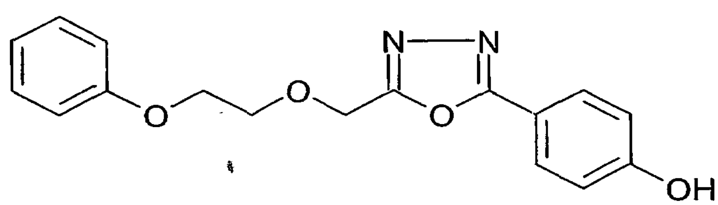
a) 4-Hydroxybenzoic acid *N'*-[2-(2-phenoxyethoxy) acetyl] hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 2-(phenoxyethoxy)acetic acid (2.0g, 10.2 mmol), 4-hydroxy benzoic hydrazide (1.55 g, 10.2 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.52 g, 10.2 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 0 to 10% MeOH:$CHCl_3$ over a thirty minute period) followed by crystallization of the isolated material from MeOH:Et_2O afforded 1.02 g (30%) of 4-hydroxybenzoic acid *N'*-[2-(2-phenoxyethoxy) acetyl] hydrazide.

^{1}H NMR (DMSO-d6) δ 10.08 (bs, 2H), 9.76 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.24-7.32 (m, 2H), 6.91-6.97 (m, 3H), 6.81 (d, 2H, J=9Hz), 4.16-4.19 (m, 2H), 4.11 (s, 2H), 3.85-3.89 (m, 2H). IR (KBr, cm^{-1}) 3229, 1695, 1647, 1627, 1609, 1588, 1574, 1507, 1498, 1246, 1140, 755. MS (ES) m/e, 331, 329. Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found C, 61.26; H, 5.51; N, 8.46.

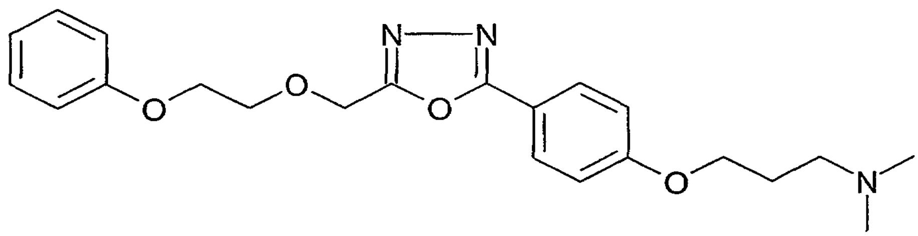
b) 4-[5-(2-Phenoxyethoxymethyl)-[1,3,4]-oxadiazol-2-yl] phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N'*-[2-(2-phenoxyethoxy) acetyl] hydrazide (0.961 g, 2.9 mmol), triphenylphosphine (1.53 g, 5.8 mmol), triethylamine (1.06 g, 10.5 mmol) and carbon tetrabromide (1.83 g, 11.9 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from EtOH afforded 0.473 g (52%) of 4-[5-(2-phenoxyethoxymethyl)-[1,3,4]-oxadiazol-2-yl] phenol.

^{1}H NMR (DMSO-d6) δ 10.32 (bs, 1H), 7.81 (d, 2H, J=9Hz), 7.23-7.30 (m, 2H), 6.89-6.97 (m, 5H), 4.85 (s, 2H), 4.13-4.16 (m, 2H), 3.89-3.92 (m, 2H). IR (KBr, cm^{-1}) 3120, 1609, 1600, 1497, 1218, 1244, 1251, 1116, 753. MS (ES) m/e, 313, 311. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found C, 65.00; H, 5.10; N, 8.65.

c) Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl) -[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

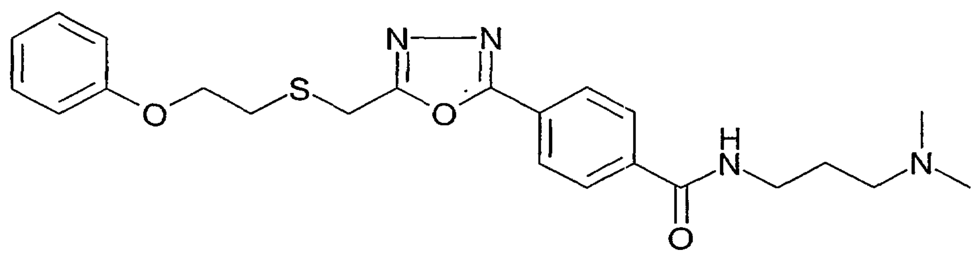


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-(2-phenoxyethoxy methyl)-[1,3,4]-oxadiazol-2-yl] phenol (0.420 g, 1.3 mmol), sodium hydride (0.124 g, 3.1 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.234 g, 1.5 mmol) to afford the title compound as a crude mixture. Crystallization from hexane:Et_2O afforded 0.321 g (60%) of dimethyl-(3-{4-[5-(2-phenoxyethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl) amine.

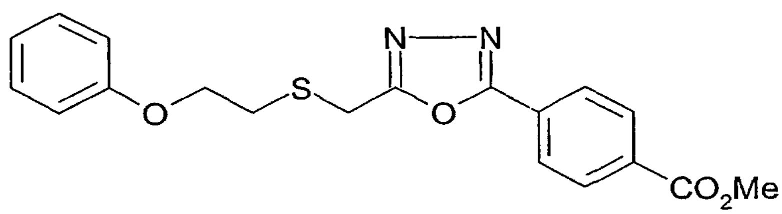
^{1}H NMR (DMSO-d6) δ 7.90 (d, 2H, J=9Hz), 7.24-7.29 (m, 2H), 7.12 (d, 2H, J=9Hz), 6.89-6.94 (m, 3H), 4.86 (s, 2H), 4.07-4.16 (m, 4H), 3.90-3.93 (m, 2H), 2.36 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.83-1.92 (m, 2H). IR ($CHCl_3$, cm^{-1}) 2948, 2824, 2777, 1614, 1600, 1589, 1499, 1469, 1302, 1256, 1175, 1087, 839. MS (FD) m/e, 397. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found C, 66.10; H, 6.83; N, 10.44. Mp(°C)=77.

Example 32

Preparation of *N*-(3-Dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzamide from (2-Phenoxyethylthio)acetic acid



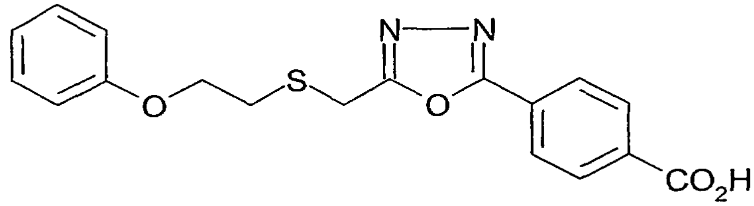
a) 4-[5-(2-Phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from (2-phenoxyethylthio)acetic acid (2.21 g, 10.4 mmol), 1,3-dicyclohexylcarbodiimide (2.15 g, 10.4 mmol) and 4-(1*H*-tetrazole-5-yl)benzoic acid methyl ester (2.13 g, 104 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 1 x 250 mL CH_2Cl_2, 3 x 250 mL 50% EtOAc:hexane) afforded 0.990 g (26%) of 4-[5-(2-phenoxyethoxy sulfanyl methyl)-[1,3,4]oxadiazol-2-yl]benzoic acid methyl ester as a crystalline solid. Purification of the remaining contaminated fractions by HPLC on silica gel (elution with a linear gradient of 25 to 40% EtOAc:hexane over a thirty minute period) afforded 0.841 g (22%) of 4-[5-(2-phenoxy ethoxy sulfanyl methyl)-[1,3,4] oxadiazol-2-yl]benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 8.09-8.16 (m, 4H), 7.23-7.30 (m, 2H), 6.90-6.94 (m, 3H), 4.26 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.91 (s, 3H), 3.04 (t, 2H, J=6Hz). IR ($CHCl_3$, cm^{-1}) 1721, 1498, 1283, 1243. MS (ES) m/e, 371. Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found C, 61.54; H, 4.91; N, 7.56.

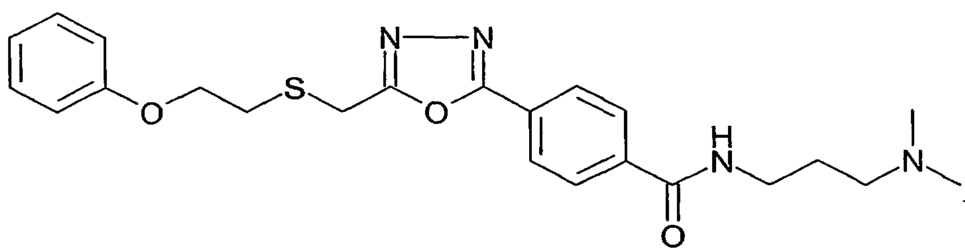
b) 4-[5-(2-Phenoxyethoxysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1c, from 4-[5-(2-phenoxy ethoxy sulfanyl methyl)-[1,3,4] oxadiazol-2-yl]benzoic acid methyl ester (1.00 g, 2.7 mmol), and lithium hydroxide (0.194 g, 8.1 mmol) to afford 0.868 g (90%) of 4-[5-(2-phenoxyethoxy sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid as a white solid.

^{1}H NMR (DMSO-d6) δ 13.35 (bs, 1H), 8.06-8.14 (m, 4H), 7.23-7.30 (m, 2H), 6.90-6.98 (m, 3H), 4.26 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.04 (t, 2H, J=6Hz). IR ($CHCl_3$, cm^{-1}). 1700, 1587, 1497, 1243. MS (ES) m/e, 357, 355. Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found C, 60.29; H, 4.51; N, 7.80.

c) *N*-(3-Dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanyl methyl)-[1,3,4]oxadiazol-2-yl]benzamide

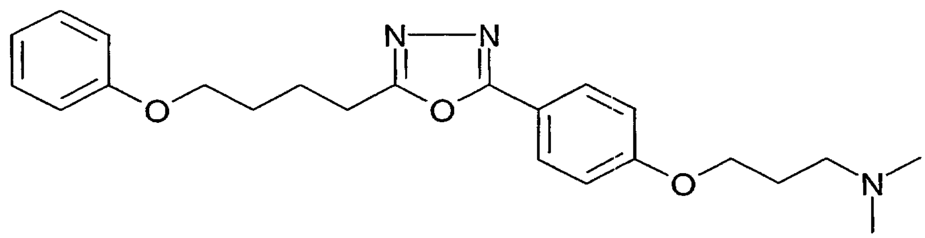


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 7c, from 4-[5-(2-phenoxyethoxy sulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.600 g, 1.68 mmol), 1-hydroxybenzotriazole (0.227 g, 1.68 mmol), 4-dimethylamino pyridine (0.021 g, 0.17 mmol), 3-(dimethylamino)propyl amine (0.181 g, 1.77 mmol) and 1,3-dicyclohexyl carbodiimide (0.365 g, 1.77 mmol) to afford the title compound as a crude mixture. Purification by radial chromatography on silica gel (elution with 10% 2M NH_3 in MeOH:CH_2Cl_2) followed by crystallization of the isolated material from EtOH:Et_2O afforded 0.335 g (45%) of *N*-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethoxysulfanyl methyl)-[1,3,4]oxadiazol-2-yl] benzamide.

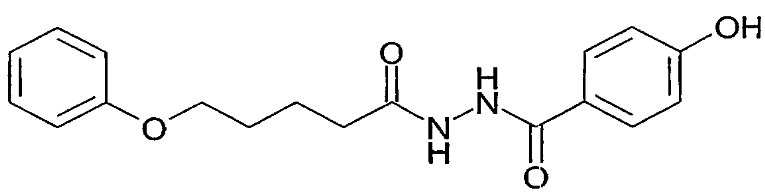
^{1}H NMR (DMSO-d6) δ 8.72 (t, 1H, J=5Hz), 8.00-8.07 (m, 4H), 7.23-7.29 (m, 2H), 6.90-6.94 (m, 3H), 4.25 (s, 2H), 4.20 (t, 2H, J=6Hz), 3.30 (q, 2H, J=6Hz), 3.04 (t, 2H, J=6Hz), 2.66 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.62-1.72 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3008, 2951, 2827, 1652, 1585, 1555, 1497, 1243, 1011. MS (ES) m/e, 441, 439. Anal. Calcd for $C_{23}H_{28}N_4O_3S$: C, 62.70; H, 6.41; N, 12.72. Found C, 62.33; H, 6.31; N, 12.62. Mp(°C)=96.

Example 33

Preparation of Dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine from 5-phenoxypentanoic acid



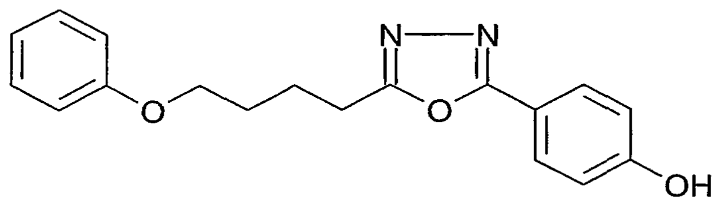
a) 4-Hydroxybenzoic acid-*N'*-(5-phenoxypentanoyl)hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 5-phenoxypentanoic acid (2.00 g, 10.3 mmol), 4-hydroxybenzoic hydrazide (1.57 g, 10.3 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.55 g, 10.3 mmol) to afford the title compound as a crude mixture. Purification by HPLC on silica gel (elution with a linear gradient of 0 to 10% MeOH:$CHCl_3$ over a thirty minute period) afforded 2.03 g (60%) of 4-hydroxybenzoic acid-*N'*-(5-phenoxypentanoyl)hydrazide as a white foam.

^{1}H NMR (DMSO-d6) δ 10.06 (bs, 1H), 10.02 (bs, 1H), 9.75 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.21-7.31 (m, 2H), 6.87-6.95 (m, 3H), 6.81 (d, 2H, J=9Hz), 3.98 (t, 2H, J=6Hz), 2.24 (t, 2H, J=7Hz), 1.62-1.83 (m, 4H). IR (KBr, cm^{-1}) 3269, 1663, 1608, 1577, 1496, 1472, 1280, 1248, 848, 754. MS (ES) m/e, 329, 327. Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found C, 65.53; H, 6.19; N, 8.36.

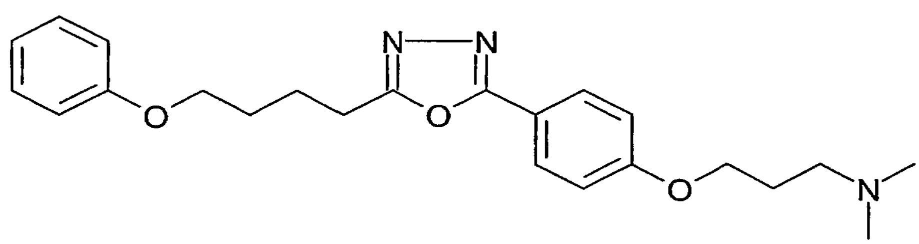
b) 4-[5-(4-Phenoxybutyl)-[1,3,4]oxadiazol-2-yl]phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid-*N'*-(5-phenoxypentanoyl)hydrazide (1.90 g, 5.8 mmol), triphenyl phosphine (11.6 g, 3.04 mmol), triethylamine (2.11 g, 20.8 mmol) and carbon tetrachloride (3.65 g, 23.7 mmol) to afford the title compound as a crude mixture. Purification by flash filtration chromatography on silica gel (elution with 50% acetone:hexane) followed by crystallization of the isolated product from ethanol afforded 1.71 g (65%) of 4-[5-(4-phenoxy butyl)-[1,3,4]oxadiazol-2-yl]phenol.

^{1}H NMR (DMSO-d6) δ 10.25 (bs, 1H), 7.78-7.82 (m, 2H), 7.23-7.31 (m, 2H), 6.88-6.96 (m, 5H), 4.02 (t, 2H, J=6Hz), 2.98 (t, 2H, J=7Hz), 1.78-1.97 (m, 4H). IR (KBr, cm^{-1}) 3061, 2935, 2870, 1611, 1601, 1499, 1283, 1245, 1229, 1174, 1035, 750, 689. MS (ES) m/e, 311, 309. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found C, 69.81; H, 5.85; N, 8.76.

c) Dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine



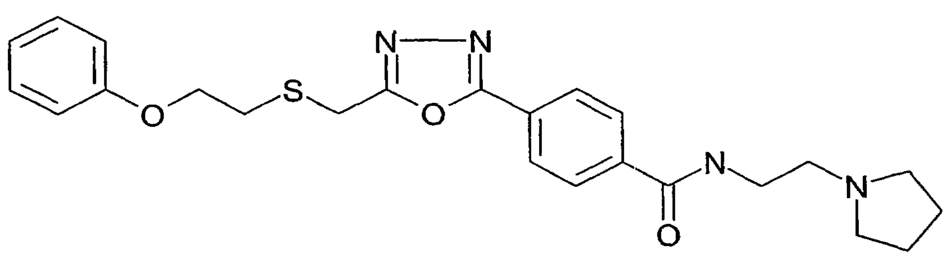
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-(4-phenoxy butyl)-[1,3,4]oxadiazol-2-yl]phenol (0.865 g, 2.8 mmol), sodium hydride (0.256 g, 6.4 mmol), and 3-chloro-N,N-dimethyl propylamine HCl (0.485 g, 3.1 mmol) to afford the title compound as a crude mixture.

Crystallization from hexane:Et_2O afforded 0.769 g (70%) of dimethyl-(3-{4-[5-(4-phenoxybutyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)amine.

^{1}H NMR (DMSO-d6) δ 7.88 (d, 2H, J=9Hz), 7.23-7.30 (m, 2H), 7.10 (d, 2H, J=9Hz), 6.89-6.94 (m, 3H), 4.08 (t, 2H, J=7Hz), 4.02 (t, 2H, J=6Hz), 2.99 (t, 2H, J=7Hz), 2.35 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.81-1.95 (m, 6H). IR ($CHCl_3$, cm^{-1}) 2952, 2873, 2825, 2777, 1615, 1589, 1500, 1470, 1248, 1174. MS (FD) m/e, 395. Anal. Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found C, 69.87; H, 7.54; N, 10.26. Mp(°C)=78.

Example 34

Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(2-aminoethyl)pyrrolidine

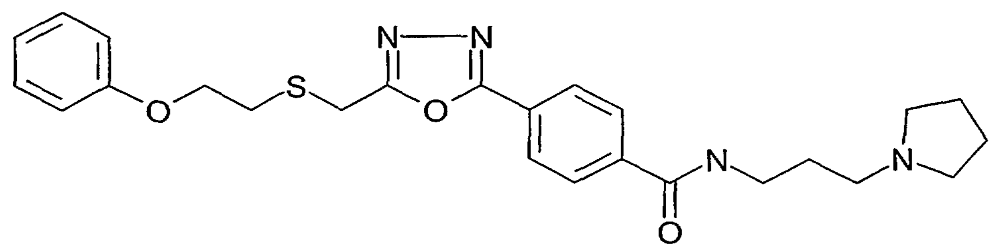


To a slurry of the 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid (0.054 g, 0.15 mmole), 1-hydroxybenzotriazole hydrate (0.024 g, 0.18 mmole), and N-(2-aminoethyl)pyrrolidine (0.023 ml, 0.18 mmole) in 2 ml dichloromethane at room temperature was added diisopropylcarbodiimide (0.047 ml, 0.30 mmole). The reaction was stirred 16 h at ambient temperature, then polystyrene methylisocyanate (0.06 mmole) and dichloromethane were added and the reaction was stirred at room temperature overnight. The reaction mixture was evaporated, taken up in 3 ml methanol, and purified over an SCX column (elution with 2 M ammonia in methanol) to afford 0.067 g (99%) of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide.

^{1}H NMR($CDCl_3$) δ 8.08(d, 2H, J=9), 7.90(d, 2H, J=9), 7.26(m, 2H), 7.01(m, 1H), 6.94(t, 1H, J=8), 6.88(d, 2H, J=9), 4.22(t, 2H, J=6), 4.07(s, 2H), 3.57(q, 2H, J=6), 3.06(t, 2H, J=6), 2.74(t, 2H, J=6), 2.60(m, 4H), 1.80(m, 4H). MS (ES) m/e, 452.19 ($C_{24}H_{28}N_4O_3S$).

Example 35

Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(3-aminopropyl)pyrrolidine



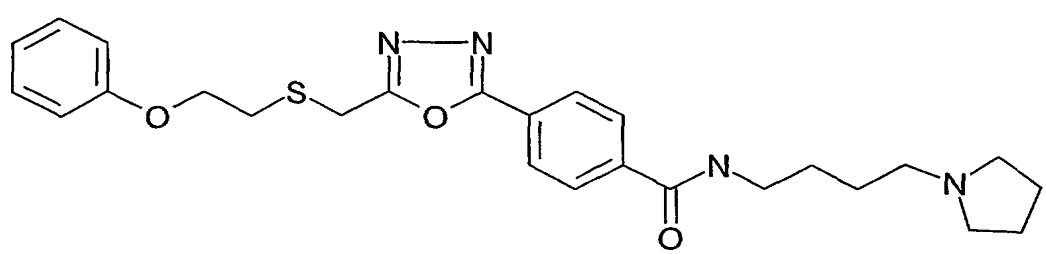
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(3-aminopropyl) pyrrolidine to afford 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide.

^{1}H NMR(CDCl3) δ 9.29(m, 1H), 8.08(d, 2H, J=9), 7.99(d, 2H, J=9), 7.27(m, 2H), 6.98(t, 1H, J=8), 6.89(d, 2H, J=7), 4.21(t, 2H, J=7), 4.07(s, 2H), 3.62(q, 2H, J=6), 3.06(t, 2H, J=6), 2.74(t, 2H, J=6), 2.59(m, 4H), 1.83(m, 6H).

MS (ES) m/e, 466.20. Anal. Calcd for $C_{25}H_{30}N_4O_3S{\cdot}0.5H_2O$: C, 63.13; H, 6.75; N, 11.78. Found C, 63.33; H, 6.26; N, 11.95.

Example 36

Preparation 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(4-pyrrolidin-1-yl-butyl)-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N-(4-aminobutyl)pyrrolidine



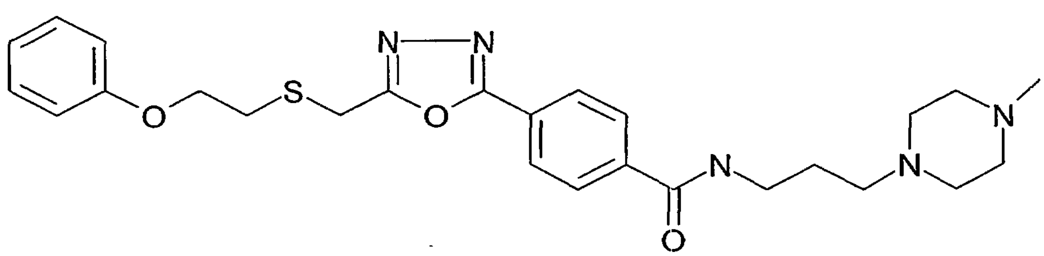
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-

yl]benzoic acid and N-(4-aminobutyl) pyrrolidine to afford 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-N-(4-pyrrolidin-1-yl-butyl)-benzamide.

^{1}H NMR($CDCl_3$) δ 8.25(m, 1H), 8.09(d, 2H, J=8), 7.88(d, 2H, J=8), 7.28(m, 2H), 6.95(t, 1H, J=7), 6.89(d, 2H, J=8), 4.22(t, 2H, J=7), 4.07(s, 2H), 3.47(q, 2H, J=7), 3.06(t, 2H, J=6), 2.48(m, 6H), 1.71(m, 8H). MS (ES) m/e, 480.22. Anal. Calcd for $C_{25}H_{30}N_4O_3S{\cdot}0.33H_2O$: C, 64.17; H, 6.77; N, 11.51. Found C, 64.16; N, 6.58; H, 11.59.

Example 37

Preparation N-[3-(4-Methyl-piperazin-1-yl)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-(4-Methyl-piperazin-1-yl)-propylamine

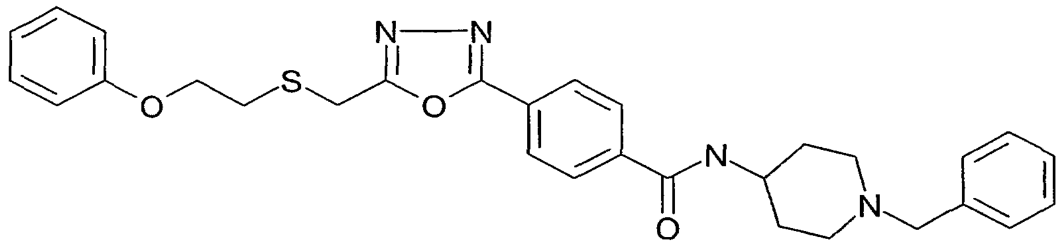


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-(4-Methyl-piperazin-1-yl)-propylamine to afford N-[3-(4-Methyl-piperazin-1-yl)-propyl]-4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.09(m, 4H), 7.26(m, 2H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.22(t, 2H, J=8), 4.07(s, 2H), 4.00(m, 1H), 3.82(m, 1H), 3.64(q, 2H, J=7), 3.40(m, 1H), 3.06(t, 2H, J=6), 2.97(m, 6H), 2.51(m, 2H), 2.12(m, 1H), 1.77(m, 5H). MS (ES) m/e, 495.23. Anal. Calcd for $C_{26}H_{33}N_5O_3S{\cdot}HCl.H_2O$: C, 56.77; H, 6.60; N, 12.73. Found C, 56.71; H, 6.82; N, 13.57.

Example 38

Preparation N-(1-Benzyl-piperidin-4-yl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 1-Benzyl-piperidin-4-ylamine

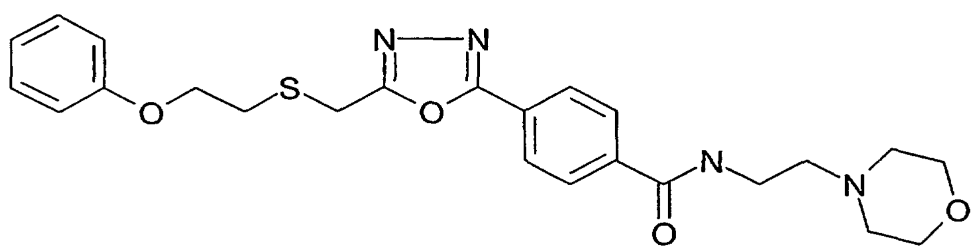


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 1-Benzyl-piperidin-4-ylamine to afford N-(1-Benzyl-piperidin-4-yl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.09(d, 2H, J=9), 7.86(d, 2H, J=9), 7.31(m, 2H), 7.24(m,5H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.21(d, 1H, J=7), 4.07(s, 2H), 4.03(m, 1H), 3.52(s, 2H), 3.06(t, 2H, J=7), 2.88(d, 2H, J=11), 2.14(t, 2H, J=10), 2.04(d, 2H, J=13), 1.58(m, 2H). MS (ES) m/e, 528.22. Anal. Calcd for $C_{30}H_{32}N_4O_3S$: C, 68.16; H, 6.10; N, 10.60. Found C, 67.78; H, 6.11; N, 10.53.

Example 39

Preparation N-(2-Morpholin-4-yl-ethyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 2-Morpholin-4-yl-ethylamine



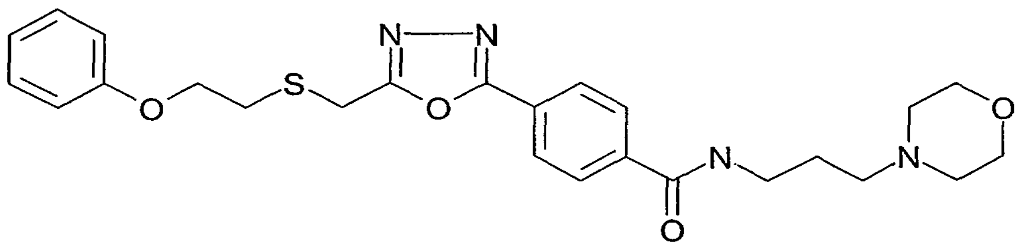
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 2-morpholin-4-yl-ethylamine to afford N-(2-Morpholin-4-yl-ethyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.11(d, 2H, J=9), 7.90(d, 2H, J=9), 7.28(m, 2H), 6.94(t, 1H, J=9), 6.89(d, 2H, J=8), 6.85(m, 1H), 4.21(t, 2H, J=7), 4.08(s, 2H), 3.75(t, 4H, J=2), 3.58(q, 2H, J=6), 3.06(t, 2H, J=6), 2.63(t, 2H, J=3), 2.52(m, 4H). MS (ES) m/e, 468.18.

Anal. Calcd for $C_{24}H_{28}N_4O_4S$: C, 61.52; H, 6.02; N, 11.96. Found C, 61.36; H, 5.94; 11.95.

Example 40

Preparation N-(3-Morpholin-4-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Morpholin-4-yl-propylamine

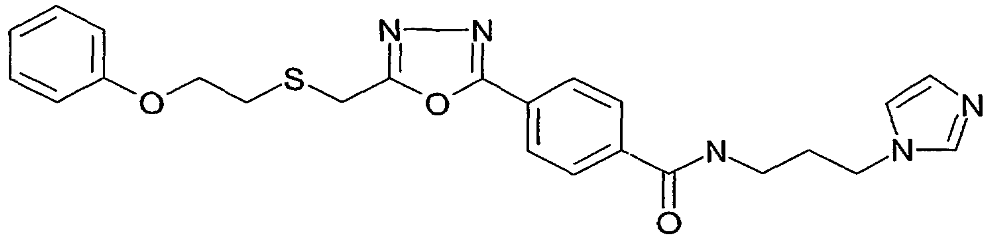


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-morpholin-4-yl-propylamine to afford N-(3-Morpholin-4-yl-propyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.29(m, 1H), 8.12(d, 2H, J=9), 7.95(d, 2H, J=9), 7.25(m, 2H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 4.22(t, 2H, J=6), 4.08(s, 2H), 3.70(t, 4H, J=6), 3.61(q, 2H, J=5), 3.06(t, 2H, J=8), 2.58(t, 2H, J=7), 2.51(m, 4H), 1.81(m, 2H, J=6). MS (ES) m/e, 482.20. Anal. Calcd for $C_{25}H_{30}N_4O_4S{\cdot}2.33H_20$: C, 57.23; H, 6.66; N, 10.68. Found C, 57.12;H, 5.69; N, 10.74.

Example 41

Preparation N-(3-Imidazol-1-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Imidazol-1-yl-propylamine

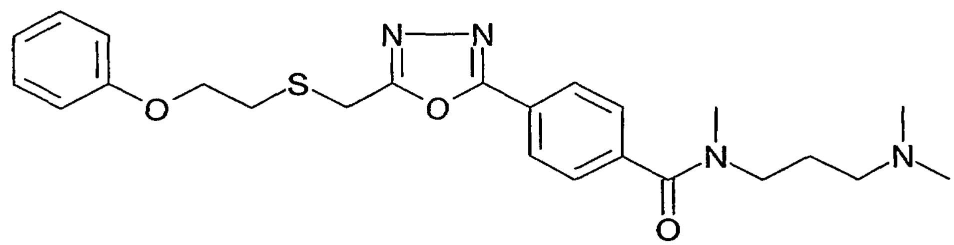


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and 3-Imidazol-1-yl-propylamine to afford N-(3-Imidazol-1-yl-propyl)-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.08(d. 2H, J=9), 7.85(d, 2H, J=9), 7.56(s, 1H), 7.26(m, 2H), 7.07(s, 1H), 6.98(s, 1H), 6.95(t, 1H, J=8), 6.89(d, 2H, J=9), 6.43(t, 1H, J=6), 4.21(t, 2H, J=7), 4.07(t, 4H, J=7), 3.51(q, 2H, J=7), 3.05(t, 2H, J=7), 2.18(m, 2H, J=7). MS (ES) m/e, 463.17.

Example 42

Preparation N-(3-Dimethylamino-propyl)-N-methyl-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N,N,N'-Trimethyl-propane-1,3-diamine

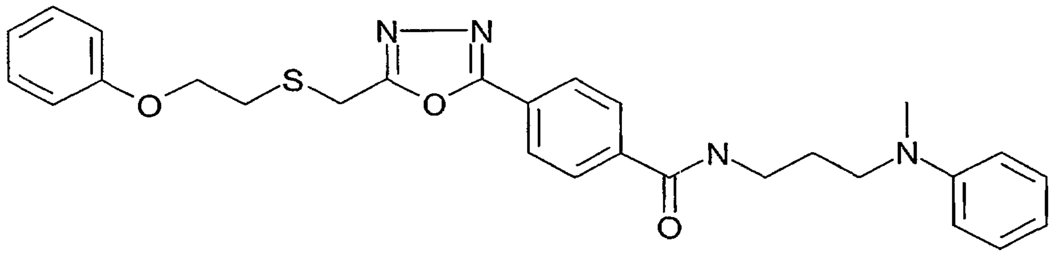


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N,N,N'-Trimethyl-propane-1,3-diamine to afford N-(3-Dimethylamino-propyl)-N-methyl-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR($CDCl_3$) δ 8.06(d, 2H, J= 9), 7.52(d, 2H, J=9), 7.25(m, 2H), 6.94(t, 1H, J=9), 6.89(d, 2H, J=9), 4.21(t, 2H, J=7), 4.07(s, 2H), 3.59(t, 1H, J=7), 3.28(t, 1H, J=8), 3.08(q, 2H, J=7), 3.06(s, 1.5H), 2.96(s, 1.5H), 2.36(t, 1H, J=9), 2.26(s, 3H), 2.10(m, 1H), 2.09(s, 3H), 1.85(m, 1H), 1.69(m, 1H). MS (ES) m/e, 454.20. Anal. Calcd for $C_{24}H_{30}N_4O_3S \cdot 0.33H_2O$: C, 62.59; H, 6.71; N, 12.16. Found C, 62.44; H, 6.54; N, 12.48.

Example 43

Preparation N-[3-(Methyl-phenyl-amino)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N1-Methyl-N1-phenyl-propane-1,3-diamine

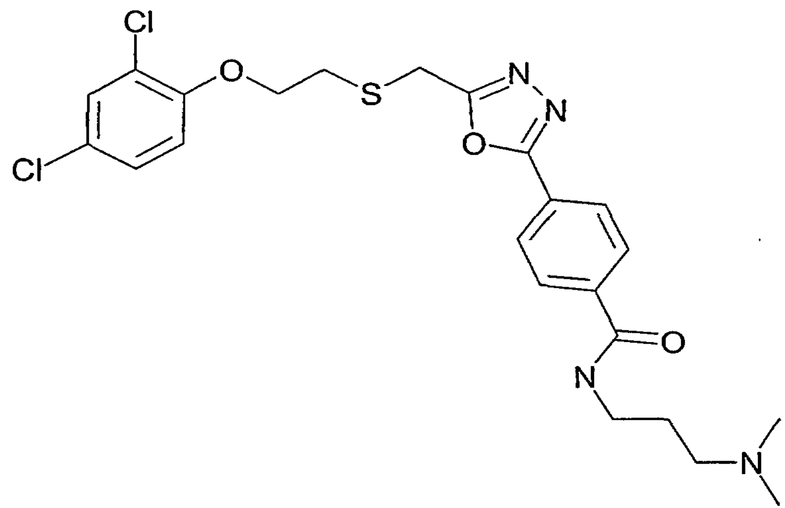


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 34, from 4-[5-(Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]benzoic acid and N1-Methyl-N1-phenyl-propane-1,3-diamine to afford N-[3-(Methyl-phenyl-amino)-propyl]-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

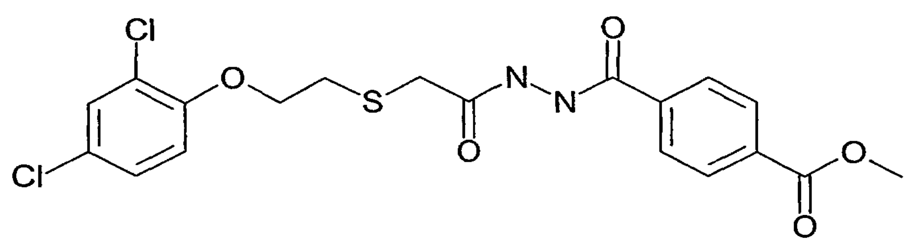
^{1}H NMR($CDCl_3$) δ 8.04(d, 2H, J=9), 7.84(d, 2H, J=9), 7.26(m, 4H), 6.95(t, 1H, J=8), 6.87(d, 2H, J=9), 6.77(m, 3H), 6.53(t, 1H, J=7), 4.21(t, 2H, J=6), 4.07(s, 2H), 3.57(q, 2H, J=7), 3.47(t, 2H, J=7), 3.06(t, 2H, J=6), 2.93(s, 3H), 1.95(m, 2H, J=7). MS (ES) m/e, 502.20. Anal. Calcd for $C_{28}H_{30}N_4O_3S{\cdot}0.33H_2O$: C, 66.12; H, 6.08; N, 11.01. Found C, 66.91; H, 5.71; N, 11.03.

Example 44

Preparation of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide



a) 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester

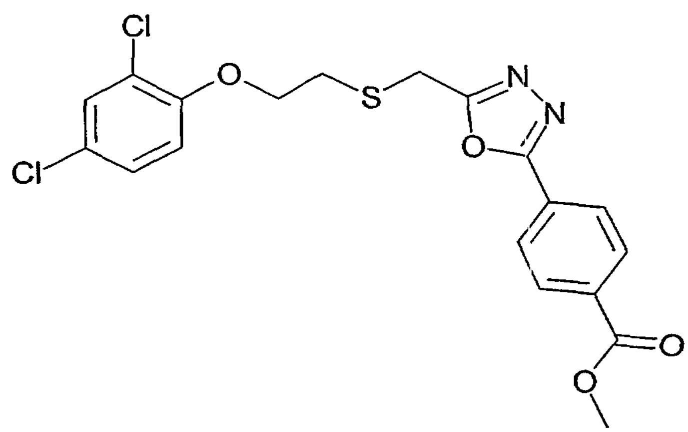


A solution of 2-[[2-(2,4-dichlorophenoxy)ethyl]-[thio]acetic acid hydrazide (1.48 g, 5.0 mmol), terephthalic acid, monomethyl ester chloride (0.993 g, 5.0 mmol), and triethylamine (0.836 mL, 6.0 mmol) in 35 mL THF was stirred at room temperature for 6 h. The resultant precipitate was collected by filtration, washed with THF, and the filtrate was concentrated in vacuo to afford an off-white solid, which was crystallized from ethanol to afford 1.94 g (85%) of 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester as a white solid (MP 156-157 °C, MW 456.03).

^{1}H NMR ($CDCl_3$) δ 9.30 (d, 1H, J=6 Hz), 8.82 (d, 1H, J=6 Hz), 8.11 (d, 2H, J=8 Hz), 7.84 (d, 2H, J=8 Hz), 7.36 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.87 (d, 1H,

J=9 Hz), 4.30 (t, 2H, J=6 Hz), 3.95 (s, 3H), 3.59 (s, 2H), and 3.16 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3193, 1714, 1604, 1568, 1481, 1465, 1295, 1105, and 869. MS (ESI) m/e 455, 457, 459, 461. Anal. Calcd for $C_{19}H_{18}Cl_2N_2O_5S$: C, 49.90; H, 3.97; Cl, 15.50; N, 6.13; S, 7.01. Found C, 49.99; H, 3.98; Cl, 15.79; N, 6.15; S, 7.37.

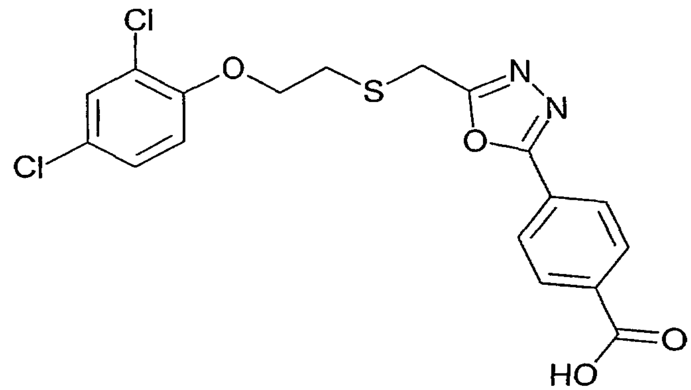
b) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester



A heterogeneous mixture of 4-(N'-{2-[2-(2,4-dichlorophenoxy)-ethylsulfanyl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester (0.228 g, 0.5 mmol), triphenylphosphine (0.265 g, 1.0 mmol), triethylamine (0.251 mL, 1.8 mmol) and carbon tetrachloride (0.202 mL, 2.06 mmol) in 4 mL acetonitrile was stirred at room temperature for 4 h. The resultant precipitate was collected by filtration, washed with acetonitrile and diethyl ether, and the solid was dried in vacuo at 40 °C for 2 h to afford 0.153 g (70%) of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester as a white solid (MP 148-152 °C, MW 438.02).

^{1}H NMR ($CDCl_3$) δ 8.17 (d, 2H, J=8 Hz), 8.10 (d, 2H, J=8 Hz), 7.34 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.84 (d, 1H, J=9 Hz), 4.26 (t, 2H, J=6 Hz), 4.18 (s, 2H), 3.97 (s, 3H), and 3.12 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 2940, 1717, 1485, 1470, 1437, 1432, 1287, 1252, 1236, 1114, 1062, 1010, 776, 719, and 715. MS (ESI) m/e 437, 439, 441, 443. Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_4S$: C, 51.95; H, 3.67; Cl, 16.14; N, 6.38; S, 7.30. Found C, 52.32; H, 3.69; Cl, 15.86; N, 6.38; S, 7.33.

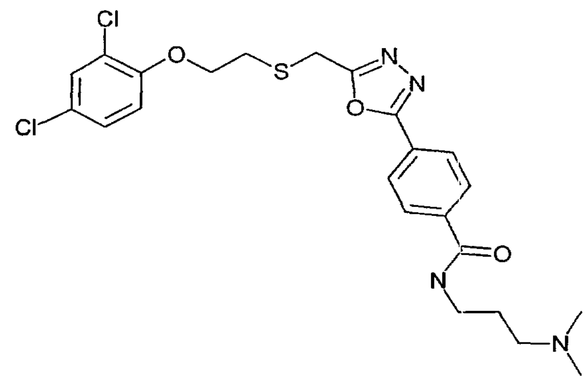
c) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid



A suspension of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester (0.22 g, 0.5 mmol), and lithium hydroxide (0.036 g, 1.5 mmol) in 3.5 mL THF and 1.5 mL H_2O was stirred at room temperature for 5 h. The THF was removed in vacuo, and the remaining aqueous solution adjusted to pH 1.7 with concentrated HCl. The resultant precipitate was collected by filtration, washed with H_2O, and dried in vacuo at 40 °C to afford 0.134 g (63%) of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid as a white solid (MP 161-163 °C, MW 424.01).

^{1}H NMR (DMSO-d_6) δ 13.30 (bs, 1H), 8.11 (d, 2H, J=9 Hz), 8.04 (d, 2H, J=9 Hz), 7.52 (d, 1H, J=2 Hz), 7.33 (dd, 1H, J=2 and 9 Hz), 7.17 (d, 1H, J=9 Hz), 4.28 (t, 2H, J=6 Hz), 4.27 (s, 2H), and 3.05 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 2910, 2670, 2550, 1704, 1686, 1551, 1485, 1433, 1291, 1262, 1072, 871, and 714. MS (ESI) m/e 423, 425, 427, 429. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_4S$: C, 50.84; H, 3.32; Cl, 16.67; N, 6.59; S, 7.54. Found C, 50.78; H, 3.40; Cl, 16.83; N, 6.55; S, 7.74.

d) 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide

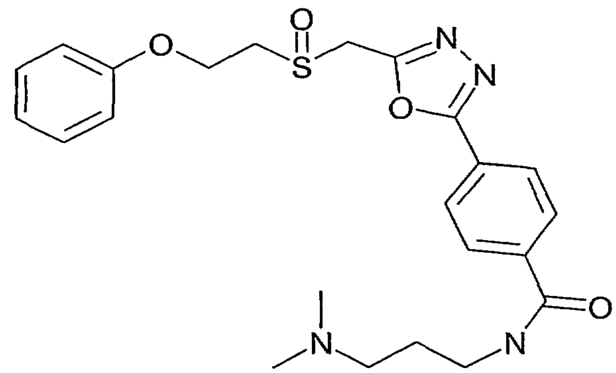


A solution of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid (0.361 g, 0.85 mmol), and 1,1'-carbonyldiimidazole (0.139 g, 0.86 mmol) in 10.0 mL THF was stirred at 60 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.129 mL, 1.02 mmol), then stirred at room temperature for 3 h. The THF was concentrated in vacuo and the resultant precipitate was collected by filtration, washed with ethyl acetate and diethyl ether, and dried in vacuo at 40 °C to afford 0.25 g (57%) of 4-{5-[2-(2,4-dichlorophenoxy)-ethylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}-N-(3-dimethylaminopropyl)-benzamide as a white solid (MP 140-141 °C, MW 508.11).

^{1}H NMR ($CDCl_3$) δ 8.86 (bs, 1H), 8.09 (d, 2H, J=9 Hz), 7.92 (d, 2H, J=9 Hz), 7.34 (d, 1H, J=2 Hz), 7.17 (dd, 1H, J=2 and 9 Hz), 6.84 (d, 1H, J=9 Hz), 4.26 (t, 2H, J=6 Hz), 4.17 (s, 2H), 3.61 (m, 2H), 3.11 (t, 2H, J=6 Hz), 2.61 (m, 2H), 2.38 (bs, 6H), 1.83 (m, 2H). IR (KBr, cm^{-1}) 3335, 2942, 2761, 2722, 1635, 1555, 1484, 1105, and 803. MS (ESI) m/e 507, 509, 511, 513. Anal. Calcd for $C_{23}H_{26}Cl_2N_4O_3S$: C, 54.23; H, 5.14; Cl, 13.92; N, 11.00; S, 6.29. Found C, 54.03; H, 5.15; Cl, 13.98; N, 10.98; S, 6.25.

Example 45

Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

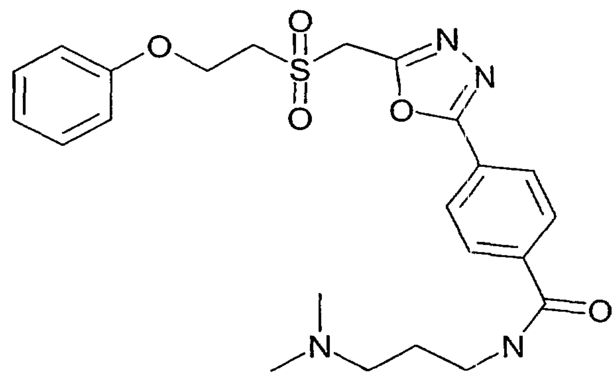


A solution of the N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide (0.044 g, 0.1 mmol)prepared in Example 32, glacial acetic acid (1.14 mL, 20.0 mmol), and 3-chloroperoxybenzoic acid (0.022 g, 0.1 mmol) in 1 mL of dichloromethane was stirred at room temperature for 1 h. The mixture was quenched with 3 mL saturated sodium sulfite followed by addition of 6 mL H_2O and 1 mL dichloromethane. The resultant biphasic solution was adjusted to pH 10.3 with 1N NaOH, the solvent layers separated, and the aqueous phase back extracted with 6x10 mL dichloromethane. The combined dichloromethane extracts were washed with H_2O and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.043 g (95%) of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid (MP 112-114 °C, MW 456.57). Analytical HPLC: 93% purity.

^{1}H NMR ($CDCl_3$) δ 8.88 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 7.95 (d, 2H, J=8 Hz), 7.30 (t, 2H, J=8 Hz), 7.01 (t, 1H, J=7 Hz), 6.93 (d, 2H, J=8 Hz), 4.62 (d, 1H, J=14 Hz), 4.48 (m, 2H), 4.36 (d, 1H, J=14 Hz), 3.61 (m, 2H), 3.40 (m, 2H), 2.65 (m, 2H), 2.41 (bs, 6H), and 1.86 (m, 2H). IR (KBr, cm^{-1}) 3344, 2922, 2761, 1636, 1549, 1497, 1251, and 1044. MS (ESI) m/e 457, 455. Anal. Calcd for $C_{23}H_{28}N_4O_4S$: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 59.91; H, 6.16; N, 11.61; S, 6.50.

Example 46

Preparation of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

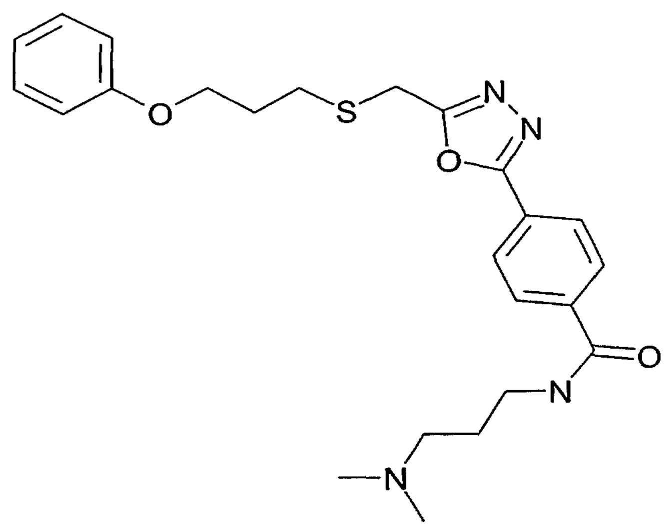


A solution of the N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide (0.022 g, 0.05 mmol) prepared in Example 32, glacial acetic acid (0.58 mL, 10.0 mmol), and 3-chloroperoxybenzoic acid (0.022 g, 0.1 mmol) in 1 mL of dichloromethane was stirred at room temperature for 19 h. The mixture was quenched with 3 mL saturated sodium sulfite followed by addition of 2 mL H_2O and 4 mL dichloromethane. The resultant biphasic solution was adjusted to pH 10.3 with 1N NaOH, the solvent layers separated, and the aqueous phase back extracted with 3x15 mL dichloromethane. The combined dichloromethane extracts were washed with H_2O and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.017 g (73%) of a mixture composed primarily of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide and a minor amount of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid. A solution of the preceding mixture (0.015 g, ~0.03 mmol), osmium tetroxide (2.5 weight percent solution in 2-methyl-2-propanol, 0.003 mL, 0.25 □M), and 4-methylmorpholine N-oxide (0.003 g, 0.025 mmol) in 1 mL of THF and 0.5 mL dichloromethane was stirred at room temperature for 1 h. The THF was removed in vacuo, the resultant gum redissolved in dichloromethane, washed with H_2O and brine, dried over anhydrous sodium sulfate, filtered, and and concentrated in vacuo to afford 0.008 g of a black solid. Purification by column chromatography on silica gel (isocratic elution with 8:2 $CHCl_3$/2.0 M ammonia in methanol) afforded 0.003 g (13%) of N-(3-dimethylaminopropyl)-4-[5-(2-phenoxyethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MW 472.57).

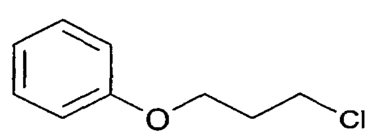
^{1}H NMR ($CDCl_3$) δ 8.88 (bs, 1H), 8.11 (d, 2H, J=8 Hz), 7.95 (d, 2H, J=8 Hz), 7.33 (t, 2H, J=8 Hz), 7.04 (t, 1H, J=7 Hz), 6.97 (d, 2H, J=8 Hz), 4.86 (s, 2H), 4.53 (t, 2H, J=5 Hz), 3.71 (t, 2H, J=5 Hz), 3.61 (m, 2H), 2.65 (m, 2H), 2.41 (bs, 6H), and 1.87 (m, 2H). MS (ESI) m/e 471, 473.

Example 47

Preparation of N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



a) 3-chloropropoxy benzene

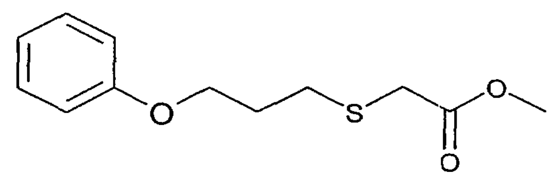


A solution of phenol (9.41 g, 0.1 M), 1-bromo-3-chloropropane (15.74 g, 0.1 M) and potassium carbonate (13.8 g, 0.1 M) in 150 mL of DMF was stirred at room temperature for 48 h, then sonicated at 50-60 °C for 12 h. The DMF was removed in vacuo, the residue diluted with EtOAc, washed with water, 5 N NaOH, and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 14.4 g (84%) of 3-chloropropoxy benzene as a clear oil.

^{1}H NMR (DMSO-d6) δ 7.3 (m, 2H), 6.9 (m, 3H), 4.1 (t, 2H, J=6 Hz), 3.6 (t, 2H, J=6 Hz), and 2.1 (quintet, 2H, J=6 Hz). IR ($CHCl_3$, cm^{-1}) 1600, 1587, 1498, 1470, 1244,

1226, 1172, and 1039. MS (EI) m/e 170. Anal. Calcd for $C_9H_{11}ClO$: C, 63.35; H, 6.50; Cl, 20.78. Found C, 65.60; H, 6.57; Cl, 17.41.

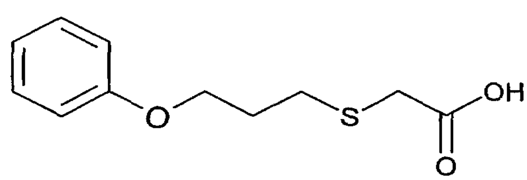
b) (3-phenoxypropylsulfanyl)-acetic acid methyl ester



A solution of 3-chloropropoxy benzene (1.00 g, 5.86 mmol), thioglycolate methyl ester (0.622 g, 5.86 mmol) and potassium carbonate (1.00 g, 7.25 mmol) in 5 mL of DMF was stirred at room temperature for 48 h, then sonicated at 50-60 °C for 8 h, then stirred at room temperature for an additional 64 h. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.29 g (92%) of (3-phenoxypropylsulfanyl)-acetic acid methyl ester as a clear oil.

^{1}H NMR (DMSO-d6) δ 7.3 (m, 2H), 6.9 (m, 3H), 4.0 (t, 2H, J=6 Hz), 3.65 (s, 3H), 3. 4 (s, 2H), 2.7 (t, 2H, J=7 Hz), and 1.9 (m, 2H). IR ($CHCl_3$, cm^{-1}) 2954, 1734, 1600, 1587, 1497, 1469, 1437, 1289, and 1244. MS (FD) m/e 241. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71. Found C, 58.81; H, 6.24.

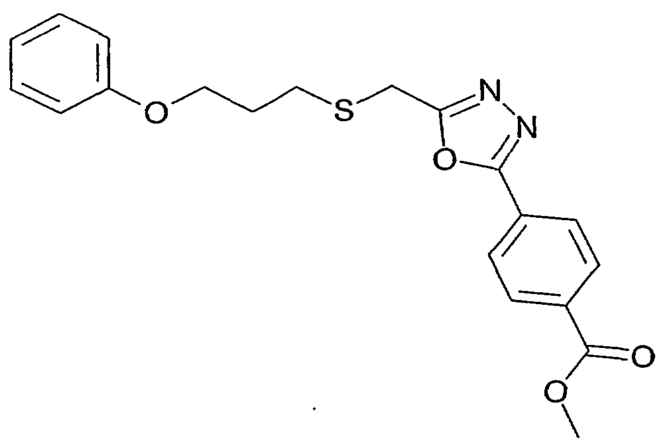
c) (3-phenoxypropylsulfanyl)-acetic acid



A solution of (3-phenoxypropylsulfanyl)-acetic acid methyl ester (1.20 g, 5.0 mmol) and 1 N NaOH(15.0 mL, 15 mmol) in 15 mL of methanol was stirred at room temperature for 48 h. The solvent was removed in vacuo, the residue triturated with EtOAc, then dissolved in 1 N HCl and EtOAc. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 0.853 g (75%) of 3-phenoxypropylsulfanyl)-acetic acid as a clear oil.

^{1}H NMR (DMSO-d6) δ 12.5 (br s, 1H), 7.3 (m, 2H), 6.9 (m, 3H), 4.0 (t, 2H, J=6 Hz), 3.3 (s, 2H), 2.7 (t, 2H, J=7 Hz), and 2.0 (quintet, 2H, J=6 Hz). IR ($CHCl_3$, cm^{-1}) 3010, 2944, 1711, 1601, 1497, 1301, 1290, 1244, and 1172. MS (ESI) m/e 227, 225. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.23; S, 14.17. Found C, 58.16; H, 6.20; S, 13.78.

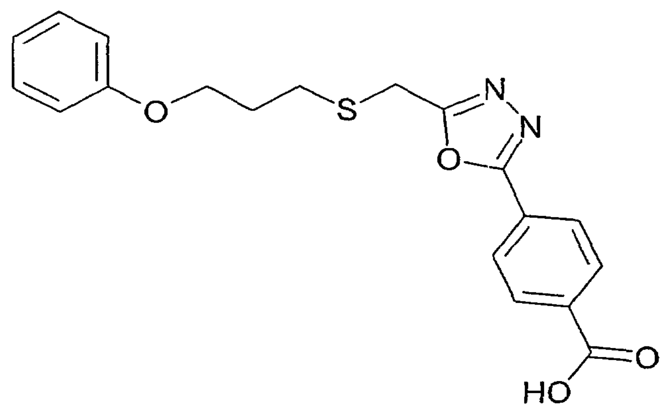
d) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1b, from 4-(1H-tetrazol-5-yl)-benzoic acid methyl ester (0.714 g, 3.5 mmol) and (3-phenoxypropylsulfanyl)-acetic acid (0.8 g, 3.54 mmol). Purification by column chromatography on silica gel (elution with linear gradient of 15-100% ethyl acetate/hexane) afforded 0.985 g (73%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester as a tan solid (MP 97-100 °C, MW 384.46).

^{1}H NMR ($CDCl_3$) δ 8.17 (d, 2H, J=9 Hz), 8.12 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.87 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=6 Hz), 3.97 (s, 3H), 3.96 (s, 2H), 2.86 (t, 2H, J=7 Hz), and 2.11 (m, 2H). IR (KBr, cm^{-1}) 2920, 1718, 1604, 1439, 1280, 1254, 1109, 755, and 709. MS (ESI) m/e 385, 383. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found C, 62.90; H, 5.77; N, 7.30; S, 8.81.

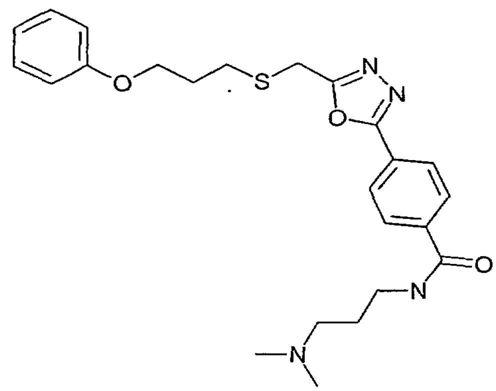
e) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



A suspension of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (0.961 g, 2.5 mmol), and lithium hydroxide (0.183 g, 7.5 mmol) in 9 mL THF and 4 mL H_2O was stirred at room temperature for 4 h. The THF was removed in vacuo, an additional 10 mL of H_2O was added, and the heterogeneous aqueous mixture was adjusted to pH 1.8 with concentrated HCl. The resultant precipitate was collected by filtration, washed with H_2O, and dried in vacuo at 40 °C to afford 0.917 g (99%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as an off-white solid (MP 180-185 °C, MW 370.43).

^{1}H NMR (DMSO-d_6) δ 13.30 (bs, 1H), 8.11 (d, 2H, J=9 Hz), 8.07 (d, 2H, J=9 Hz), 7.23 (t, 2H, J=8 Hz), 6.88 (m, 3H), 4.15 (s, 2H), 4.01 (t, 2H, J=6 Hz), 2.78 (t, 2H, J=7 Hz), and 1.99 (m, 2H). IR (KBr, cm^{-1}) 2997, 2643, 2522, 1709, 1471, 1267, 1242, 753, and 714. MS (ESI) m/e 371, 369. Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56; S, 8.66. Found C, 62.26; H, 5.52; N, 7.54; S, 8.29.

f) N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

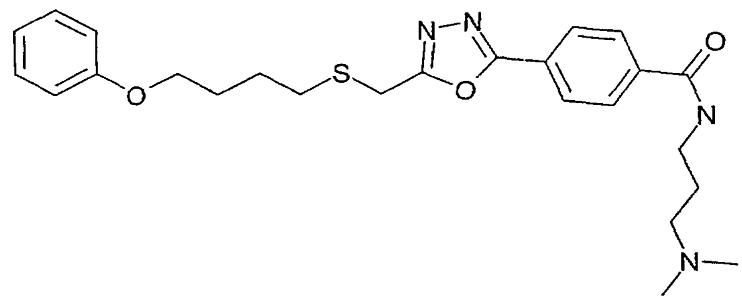


A solution of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.37 g, 1.0 mmol), and 1,1'-carbonyldiimidazole (0.164 g, 1.01 mmol) in 10.0 mL THF was stirred at 60 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.152 mL, 1.2 mmol), then stirred at room temperature for 6 h. The THF was concentrated in vacuo, and the oily residue redissolved in ethyl acetate/H_2O. The solvent layers were separated, and the ethyl acetate layer was washed with H_2O and brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo to afford 0.342 g of a tan solid. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 $CHCl_3$/2.0 M ammonia in methanol) afforded 0.256 g (56%) of N-(3-dimethylaminopropyl)-4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 77-80 °C, MW 454.60).

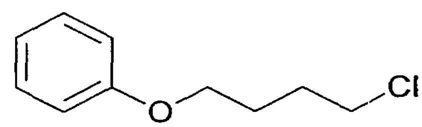
^{1}H NMR ($CDCl_3$) δ 8.79 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 8.01 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=8 Hz), 6.92 (t, 1H, J=7 Hz), 6.88 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=6 Hz), 3.95 (s, 2H), 3.64 (m, 2H), 2.86 (t, 2H, J=7 Hz), 2.77 (m, 2H), 2.52 (bs, 6H), 2.11 (m, 2H), and 1.96 (m, 2H). IR (KBr, cm^{-1}) 3304, 3063, 2937, 2814, 2762, 1633, 1586, 1561, 1554, 1541, 1499, 1469, 1245, 1183, 853, and 751. MS (ESI) m/e 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65; N, 12.32; S, 7.05. Found C, 63.29; H, 6.67; N, 12.34; S, 7.03.

Example 48

Preparation of N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



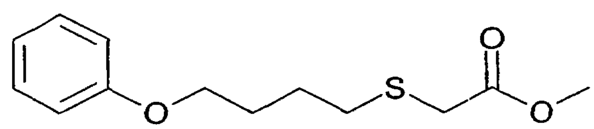
a) 4-chlorobutoxy benzene



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47a, from phenol (4.75 g, 50.0 mmol) and 1-bromo-4-chlorobutane (5.82 mL, 50.0 mmol) to afford 9.5 g (quantitative) of 4-chlorobutoxy benzene as a colorless oil (MW 184.67).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.00 (t, 2H, J=6 Hz), 3.62 (t, 2H, J=6 Hz), and 1.97 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3012, 2960, 2875, 1599, 1587, 1498, 1471, 1244, and 1172. MS (EI) m/e 184. Anal. Calcd for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10; Cl, 19.20. Found C, 64.96; H, 7.03; Cl, 18.91.

b) (4-phenoxybutylsulfanyl)-acetic acid methyl ester

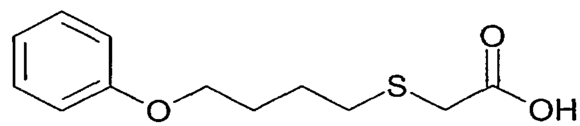


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47b, from 4-chlorobutoxy benzene (1.85 g, 10.0 mmol) and methyl thioglycolate (1.03 mL, 11.0 mmol) to afford 2.46g (96%) of (4-phenoxybutylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 254.35).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.93 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.73 (s, 3H), 3.24 (s, 2H), 2.72 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3012, 2930, 1733, 1600, 1497, 1287, and 1244. MS (FD) m/e 254.

Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; S, 12.61. Found C, 60.43; H, 7.06; S, 10.84.

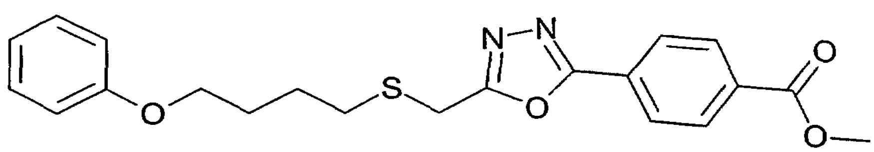
c) (4-phenoxybutylsulfanyl)-acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47c, from 4-phenoxybutylsulfanyl)-acetic acid methyl ester (2.29 g, 9.0 mmol) and 2N NaOH (13.5 mL, 27.0 mmol) to afford 2.04g (94%) of (4-phenoxybutylsulfanyl)-acetic acid as a pale yellow solid (MP 48-50 °C, MW 240.32).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.28 (s, 2H), 2.74 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3010, 2944, 1710, 1600, 1497, 1300, 1291, 1244, and 1172. MS (ESI) m/e 241, 239. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found C, 58.55; H, 6.66; S, 16.01.

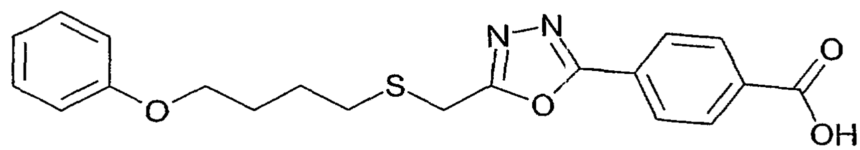
d) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47d, from 4-(1H-tetrazol-5-yl)-benzoic acid methyl ester (0.817 g, 4.0 mmol) and (4-phenoxybutylsulfanyl)-acetic acid (0.971 g, 4.04 mmol). Purification by column chromatography on silica gel (elution with linear gradient of 10-100% ethyl acetate/hexane) afforded 1.08 g (68%) of 4-[5-(4-phenoxybutylsulfanylmethyl) -[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester as an off-white solid (MP 98-105 °C, MW 398.48).

^{1}H NMR ($CDCl_3$) δ 8.17 (d, 2H, J=9 Hz), 8.13 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.92 (t, 1H, J=8 Hz), 6.86 (d, 2H, J=8 Hz), 3.96 (m, 7H), 2.73 (t, 2H, J=7 Hz), and 1.87 (m, 4H). IR (KBr, cm^{-1}) 2930, 1713, 1554, 1498, 1426, 1289, 1283, 1241, 1119, 1112, 754, and 713. MS (ESI) m/e 399, 397. Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03; S, 8.05. Found C, 63.41; H, 6.04; N, 6.82; S, 7.97.

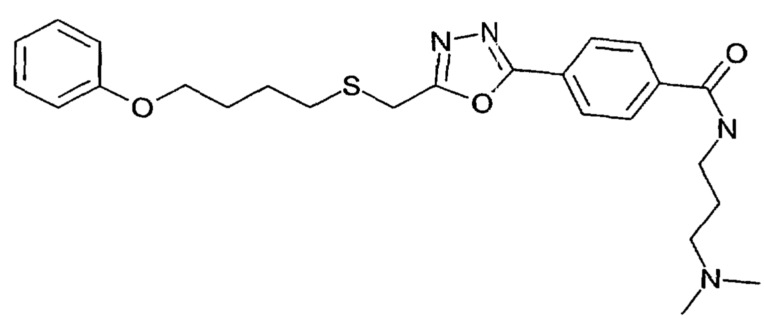
e) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47e, from 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (1.04 g, 2.6 mmol), and lithium hydroxide (0.191 g, 7.8 mmol) to afford 1.0 g (quantitative) of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as an off-white solid (MP 153-160 °C, MW 384.46).

^{1}H NMR (DMSO-d_6) δ 13.25 (bs, 1H), 8.11 (d, 2H, J=9 Hz), 8.08 (d, 2H, J=9 Hz), 7.22 (t, 2H, J=8 Hz), 6.87 (m, 3H), 4.12 (s, 2H), 3.93 (t, 2H, J=6 Hz), 2.69 (t, 2H, J=7 Hz), and 1.73 (m, 4H). IR (KBr, cm^{-1}) 3314, 2925, 2851, 1705, 1684, 1498, 1293, 1247, 748, and 715. MS (ESI) m/e 385, 383. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found C, 63.19; H, 5.99; N, 7.13; S, 8.37.

f) N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



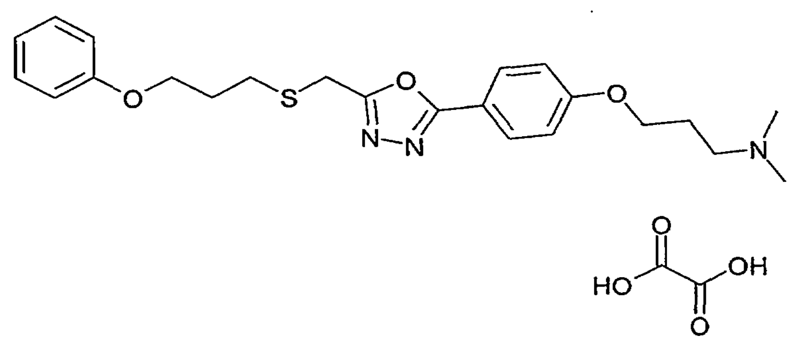
A solution of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.384 g, 1.0 mmol), and 1,1'-carbonyldiimidazole (0.164 g, 1.01 mmol) in 8.0 mL

THF was stirred at 65 °C for 0.5 h. The reaction solution was allowed to cool to ambient temperature followed by addition of 3-(dimethylamino)propylamine (0.152 mL, 1.2 mmol), then stirred at room temperature for 4.5 h. The THF was concentrated in vacuo, and the oily residue redissolved in 5-10% THF/ethyl acetate and H_2O. The solvent layers were separated, and the ethyl acetate/THF layer was washed with H_2O, saturated aqueous $NaHCO_3$ solution, and brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo to afford 0.334 g of a tan solid. Crystallization from EtOH/diethyl ether afforded 0.182 g (39%) of N-(3-dimethylaminopropyl)-4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 87-93 °C, MW 468.62).

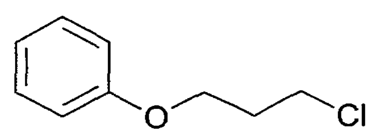
^{1}H NMR ($CDCl_3$) δ 8.75 (bs, 1H), 8.12 (d, 2H, J=8 Hz), 8.03 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=8 Hz), 6.92 (t, 1H, J=7 Hz), 6.86 (d, 2H, J=8 Hz), 3.96 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.64 (m, 2H), 2.83 (m, 2H), 2.73 (t, 2H, J=7 Hz), 2.56 (bs, 6H), 1.99 (m, 2H), and 1.86 (m, 4H). IR (KBr, cm^{-1}) 3341, 2941, 2764, 1640, 1552, 1536, and 1244. MS (ESI) m/e 467, 469. Anal. Calcd for $C_{25}H_{32}N_4O_3S$: C, 64.08; H, 6.88; N, 11.96; S, 6.84. Found C, 63.76; H, 6.97; N, 11.56; S, 6.72.

Example 49

Preparation of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt

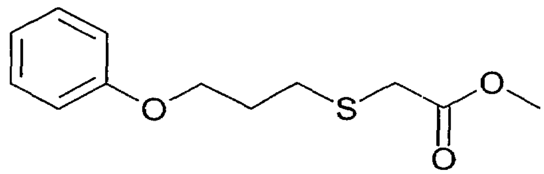


a) 3-chloropropoxy benzene



The above compound was prepared as exemplified in Example 47a.

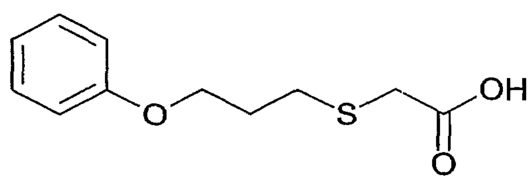
b) (3-phenoxypropylsulfanyl)-acetic acid methyl ester



The above compound was prepared as exemplified in Example 47b from 3-chloropropoxy benzene (3.41 g, 20.0 mmol) and methyl thioglycolate (2.07 mL, 22.0 mmol). Purification by column chromatography on silica gel (isocratic elution with 10% ethyl acetate/toluene) afforded 2.95g (61%) of (3-phenoxypropylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 240.32).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.93 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=6 Hz), 3.73 (s, 3H), 3.25 (s, 2H), 2.84 (t, 2H, J=7 Hz), and 2.08 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3010, 2954, 1734, 1601, 1497, 1437, 1288, 1244, and 1225. MS (ESI) m/e 241. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found C, 59.22; H, 6.71; S, 18.00.

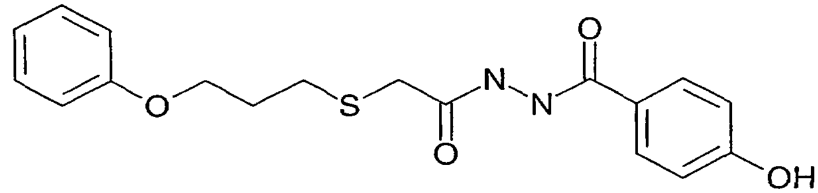
c) (3-phenoxypropylsulfanyl)-acetic acid



The above compound was prepared as exemplified in Example 47c from (3-phenoxypropylsulfanyl)-acetic acid methyl ester (2.64 g, 11.0 mmol) and 2N NaOH (16.5 mL, 33.0 mmol) to afford 2.33g (94%) of (3-phenoxypropylsulfanyl)-acetic acid as a white crystalline solid (MP 35-37 °C, MW 226.30).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=6 Hz), 3.28 (s, 2H), 2.87 (t, 2H, J=7 Hz), and 2.11 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3041, 2927, 2674, 2565, 1710, 1601, 1498, 1244, 1172 and 1040. MS (ESI) m/e 227, 225. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S, 14.17. Found C, 57.95; H, 6.08; S, 14.11.

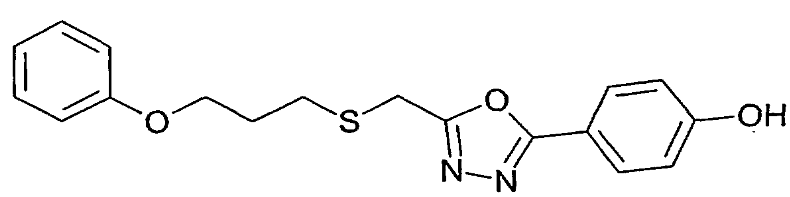
d) 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide



A solution of (3-phenoxypropylsulfanyl)-acetic acid (1.13 g, 5.0 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1.25 g, 5.0 mmol) in 5.0 mL THF and 20.0 mL acetonitrile was stirred at ambient temperature for 1.0 h followed by addition of 4-hydroxybenzoic hydrazide (0.776 g, 5.0 mmol), then stirred at room temperature for 66 h. The THF/acetonitrile were concentrated in vacuo and the resultant off-white solid redissolved in 20% THF/ethyl acetate. The ethyl acetate/THF solution was washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$ solution, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford an off-white solid. The solid was triturated with a mixture of CH_2Cl_2/diethyl ether/n-hexane, filtered, and the collected solid washed with diethyl ether and n-hexane to afford 1.53 g (85%) of 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide as an amorphous white solid (MP 146-151 °C, MW 360.44).

^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 10.07 (s, 1H), 9.96 (s, 1H), 7.73 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.91 (m, 3H), 6.79 (d, 2H, J=8 Hz), 4.02 (t, 2H, J=6 Hz), 3.22 (s, 2H), 2.78 (t, 2H, J=7 Hz), and 2.00 (m, 2H). IR (KBr, cm^{-1}) 3304, 3228, 1667, 1607, 1575, 1514, 1498, 1468, 1277, 1250, 1235, and 755. MS (ESI) m/e 361, 359. Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found C, 59.94; H, 5.62; N, 7.73; S, 8.92.

e) 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol

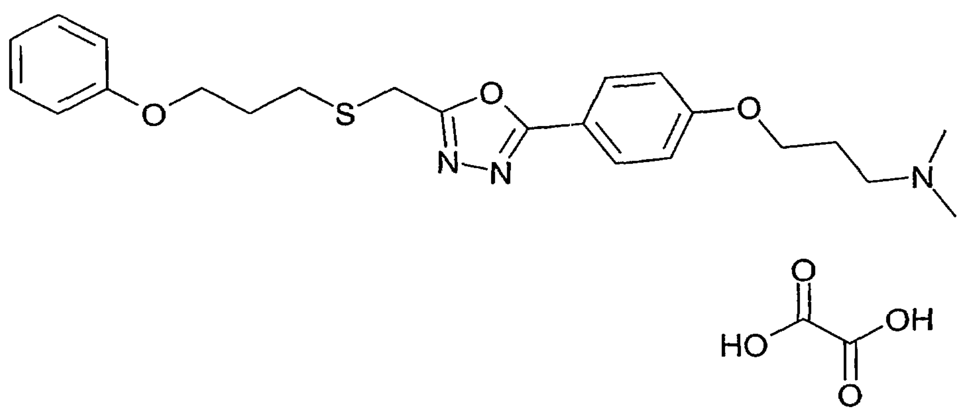


A heterogeneous mixture of 4-hydroxy-benzoic acid N'-[2-(3-phenoxypropylsulfanyl)-acetyl]-hydrazide (1.44 g, 4.0 mmol), triphenylphosphine (2.12 g, 8.0 mmol), triethylamine (2.0 mL, 14.4 mmol) and carbon tetrachloride (1.61 mL, 16.5

mmol) in 20 mL acetonitrile was stirred at room temperature for 2.5 h. The resultant precipitate was collected by filtration, washed with acetonitrile and discarded. The filtrate was concentrated in vacuo and the resultant solid redissolved in 10% THF/ethyl acetate. The ethyl acetate/THF solution was washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$ solution, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 3.92 g of a yellow oil. Purification by column chromatography on silica gel (elution with linear gradient of 0-100% ethyl acetate/toluene) afforded 1.15 g (83%) of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 122-127 °C, MW 342.42).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.96 (d, 2H, J=9 Hz), 6.93 (t, 1H, J=8 Hz), 6.87 (d, 2H, J=8 Hz), 4.05 (t, 2H, J=6 Hz), 3.92 (s, 2H), 2.85 (t, 2H, J=7 Hz), and 2.10 (m, 2H). IR (KBr, cm^{-1}) 3442, 3127, 2944, 1609, 1599, 1586, 1497, 1472, 1246, 1229, 1174, and 756. MS (ESI) m/e 343, 341. Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found C, 63.31; H, 5.32; N, 8.14; S, 9.17.

f) Dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



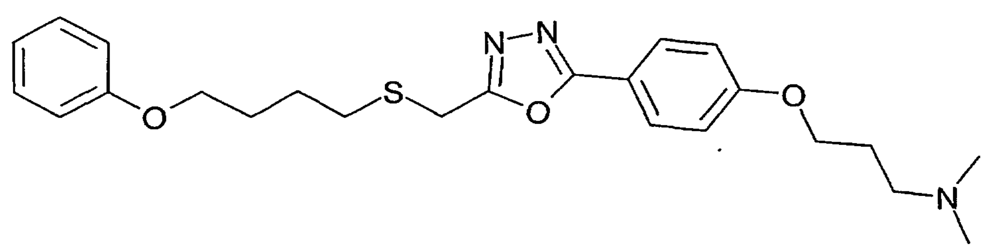
A heterogeneous mixture of 4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.342 g, 1.0 mmol), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.174 g, 1.1 mmol), and sodium hydride (0.092 g, 2.3 mmol) in 10 mL DMF was stirred at 100 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H_2O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed

with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.332 g of a yellow oil. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 $CHCl_3$/2.0 M ammonia in methanol) afforded 0.188 g (44%) of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an oily gum. The gum (0.182 g, 0.426 mmol) was dissolved in 2 mL acetone, and oxalic acid (0.042 g, 0.468 mmol), dissolved in 1 mL acetone, was added with rapid stirring at room temperature. Filtered the resultant thick precipitate, washed the collected solid with acetone and diethyl ether, and dried in vacuo at 40 °C to afford 0.205 g (93%) of dimethyl-(3-{4-[5-(3-phenoxypropylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt as a white solid (MP 131-133 °C, MW oxalate salt 517.61, MW free amine 427.57).

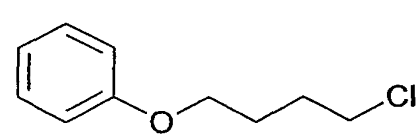
^{1}H NMR (DMSO-d_6) δ 7.91 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=8 Hz), 7.12 (d, 2H, J=9 Hz), 6.89 (m, 3H), 4.12 (t, 2H, J=6 Hz), 4.09 (s, 2H), 4.01 (t, 2H, J=6 Hz), 3.13 (m, 2H), 2.76 (t, 2H, J=7 Hz), 2.74 (s, 6H), 2.10 (m, 2H), and 1.99 (t, 2H, J=7 Hz). IR (KBr, cm^{-1}) 3042, 2928, 1723, 1611, 1499, 1472, 1259, 1248, 1177, 756, and 696. MS (ESI) m/e 428. Anal. Calcd for $C_{23}H_{29}N_3O_3S{\cdot}C_2H_2O_4$: C, 58.01; H, 6.04; N, 8.12; S, 6.19. Found C, 57.72; H, 6.01; N, 7.78; S, 6.55.

Example 50

Preparation of dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



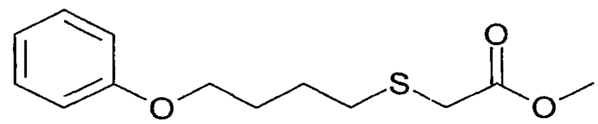
a) 4-chlorobutoxy benzene



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47a, from phenol (4.75 g, 50.0 mmol) and 1-bromo-4-chlorobutane (5.82 mL, 50.0 mmol) to afford 9.5 g (quantitative) of 4-chlorobutoxy benzene as a colorless oil (MW 184.67).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.00 (t, 2H, J=6 Hz), 3.62 (t, 2H, J=6 Hz), and 1.97 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3012, 2960, 2875, 1599, 1587, 1498, 1471, 1244, and 1172. MS (EI) m/e 184. Anal. Calcd for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10; Cl, 19.20. Found C, 64.96; H, 7.03; Cl, 18.91.

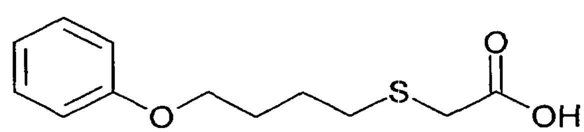
b) (4-phenoxybutylsulfanyl)-acetic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47b, from 4-chlorobutoxy benzene (1.85 g, 10.0 mmol) and methyl thioglycolate (1.03 mL, 11.0 mmol) to afford 2.46g (96%) of (4-phenoxybutylsulfanyl)-acetic acid methyl ester as a colorless oil (MW 254.35).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.93 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.73 (s, 3H), 3.24 (s, 2H), 2.72 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3012, 2930, 1733, 1600, 1497, 1287, and 1244. MS (FD) m/e 254. Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; S, 12.61. Found C, 60.43; H, 7.06; S, 10.84.

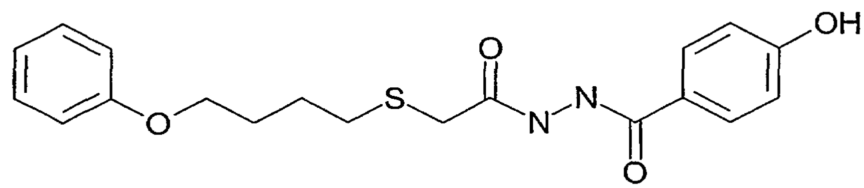
c) (4-phenoxybutylsulfanyl)-acetic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47c, from 4-phenoxybutylsulfanyl)-acetic acid methyl ester (2.29 g, 9.0 mmol) and 2N NaOH (13.5 mL, 27.0 mmol) to afford 2.04g (94%) of (4-phenoxybutylsulfanyl)-acetic acid as a pale yellow solid (MP 48-50 °C, MW 240.32).

^{1}H NMR ($CDCl_3$) δ 7.28 (t, 2H, J=8 Hz), 6.94 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 3.98 (t, 2H, J=6 Hz), 3.28 (s, 2H), 2.74 (t, 2H, J=7 Hz), and 1.86 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3010, 2944, 1710, 1600, 1497, 1300, 1291, 1244, and 1172. MS (ESI) m/e 241, 239. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found C, 58.55; H, 6.66; S, 16.01.

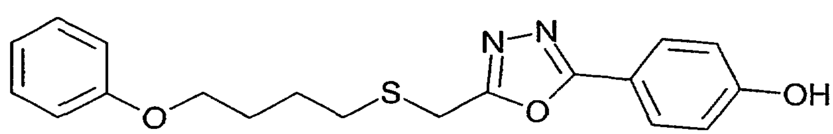
d) 4-hydroxy-benzoic acid N'-[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49d, from (4-phenoxybutylsulfanyl)-acetic acid (0.961 g, 4.0 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (0.999 g, 4.0 mmol), and 4-hydroxybenzoic hydrazide (0.621 g, 4.0 mmol) to afford 1.14 g (76%) of 4-hydroxy-benzoic acid N'-[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide as an amorphous white solid (MP 113-115 °C, MW 374.46).

^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 10.07 (s, 1H), 9.94 (s, 1H), 7.73 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=8 Hz), 6.89 (m, 3H), 6.79 (d, 2H, J=8 Hz), 3.96 (t, 2H, J=6 Hz), 3.19 (s, 2H), 2.70 (t, 2H, J=7 Hz), and 1.74 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3281, 3003, 2940, 1631, 1609, 1587, 1497, 1470, 1387, 1279, 1244, and 1171. MS (ESI) m/e 375, 373. Anal. Calcd for $C_{19}H_{22}N_2O_4S$: C, 60.94; H, 5.92; N, 7.48; S, 8.56. Found C, 60.24; H, 5.92; N, 7.50; S, 9.12.

e) 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol

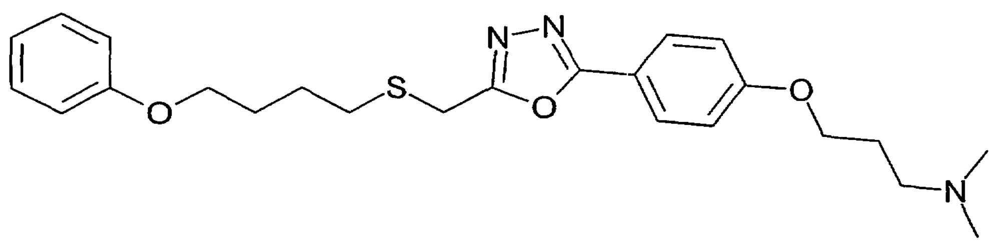


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, using 4-hydroxybenzoic acid N'-[2-(4-phenoxybutylsulfanyl)-acetyl]-hydrazide (1.09 g, 2.9 mmol), triphenylphosphine (1.54 g,

5.8 mmol), and triethylamine (1.46 mL, 10.44 mmol) to afford 0.831 g (80%) of 4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 129-130 °C, MW 356.45).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.95 (d, 2H, J=9 Hz), 6.93 (t, 1H, J=8 Hz), 6.86 (d, 2H, J=8 Hz), 3.96 (t, 2H, J=6 Hz), 3.91 (s, 2H), 2.71 (t, 2H, J=7 Hz), and 1.85 (m, 4H). IR (KBr, cm^{-1}) 3096, 2935, 1610, 1600, 1567, 1498, 1475, 1456, 1284, 1275, 1237, 1178, 757, and 691. MS (ESI) m/e 357, 355. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found C, 63.81; H, 5.68; N, 7.84; S, 9.09.

f) [Dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



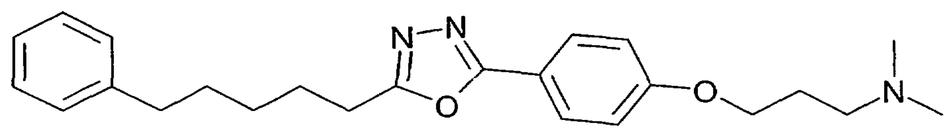
A heterogeneous mixture of 4-[5-(4-phenoxybutylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.178 g, 0.5 mmol), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.087 g, 0.55 mmol), and sodium hydride (0.046 g, 1.15 mmol) in 5 mL DMF was stirred at 100 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H_2O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.223 g of a tan solid. Purification by column chromatography on silica gel (isocratic elution with 1:1 toluene/ethyl acetate followed by 9:1 $CHCl_3$/2.0 M ammonia in methanol) afforded 0.15 g (68%) of dimethyl-(3-{4-[5-(4-phenoxybutylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 69-73 °C, MW 441.60).

^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.97 (d, 2H, J=9 Hz), 6.92 (t, 1H, J=7 Hz), 6.87 (d, 2H, J=8 Hz) 4.13 (t, 2H, J=6 Hz), 3.96 (t, 2H, J=6 Hz), 3.91 (s, 2H), 2.92 (m, 2H), 2.72 (t, 2H, J=7 Hz), 2.60 (bs, 6H), 2.25 (m, 2H), and 1.84 (m,

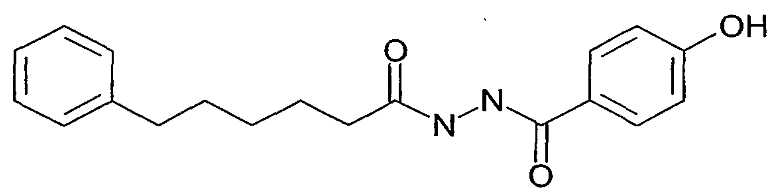
4H). IR (KBr, cm^{-1}) 2947, 1612, 1501, 1468, 1258, and 749. MS (ESI) m/e 442, 440. Anal. Calcd for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52; S, 7.26. Found C, 65.36; H, 7.12; N, 9.38; S, 7.39.

Example 51

Preparation of dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



a) 4-hydroxybenzoic acid N'-(6-phenylhexanoyl)-hydrazide

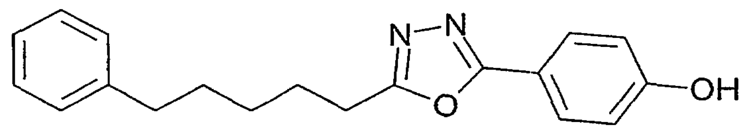


A solution of 6-phenylhexanoic acid (0.961 g, 5.0 mmol), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1.25 g, 5.0 mmol) in 5.0 mL THF and 20.0 mL acetonitrile was stirred at ambient temperature for 1.0 h followed by addition of 4-hydroxy-benzoic hydrazide (0.776 g, 5.0 mmol), then stirred at room temperature for 18 h followed by heating at 65 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature, the THF/acetonitrile were concentrated in vacuo, and the resultant gold oil redissolved in ethyl acetate. The ethyl acetate solution was washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$ solution, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford an off-white solid. The solid was triturated with a mixture of CH_2Cl_2/diethyl ether/n-hexane, filtered, and the collected solid washed with diethyl ether and n-hexane to afford 1.16 g (71%) of 4-hydroxy-benzoic acid N'-(6-phenylhexanoyl)-hydrazide as an amorphous white solid (MP 155-160 °C, MW 326.40).

^1H NMR (DMSO-d_6) δ 10.04 (s, 1H), 9.98 (s, 1H), 9.69 (s, 1H), 7.72 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=8 Hz), 7.16 (m, 3H), 6.79 (d, 2H, J=8 Hz), 2.55 (t, 2H, J=8 Hz), 2.14 (t, 2H, J=7 Hz), 1.56 (m, 4H) and 1.32 (m, 2H). IR (KBr, cm^{-1}) 3314, 3222, 3023, 2930, 2856, 1699, 1626, 1609, 1584, 1517, 1492, 1287, 1237, and 697. MS (ESI) m/e 327, 325.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found C, 69.83; H, 6.66; N, 8.43.

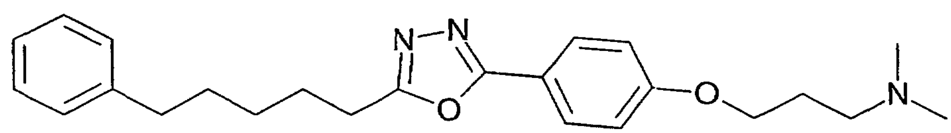
b) 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(6-phenylhexanoyl)-hydrazide (1.1 g, 3.4 mmol), triphenylphosphine (1.8 g, 6.8 mmol), and triethylamine (1.71 mL, 12.24 mmol) to afford 0.841 g (80%) of 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 118-123 °C, MW 308.38).

^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=8 Hz), 2.91 (t, 2H, J=7 Hz), 2.63 (t, 2H, J=8 Hz), 1.86 (m, 2H), 1.68 (m, 2H), and 1.48 (m, 2H). IR (KBr, cm^{-1}) 2921, 1610, 1600, 1496, 1283, and 1231. MS (ESI) m/e 309, 307. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found C, 73.52; H, 6.40; N, 8.66.

c) Dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



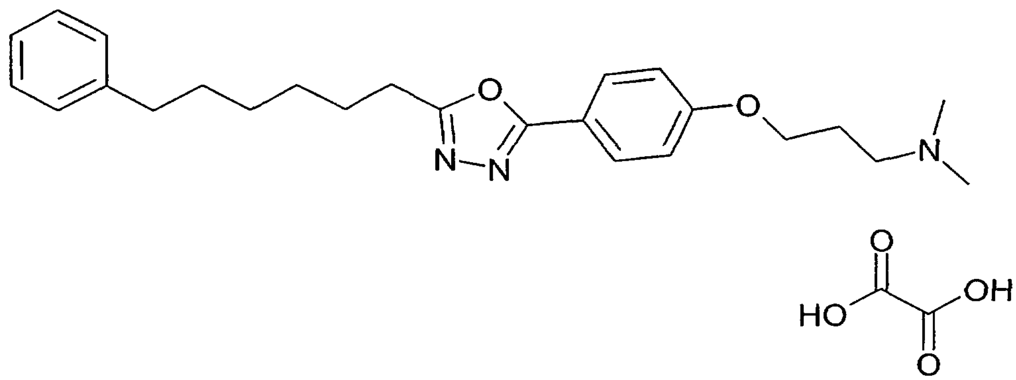
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.154 g, 0.5 mmol) to afford 0.119 g (60%) of dimethyl-(3-{4-[5-(5-phenylpentyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 49-50 °C, MW 393.53).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=7 Hz), 7.18 (m, 3H), 6.98 (d, 2H, J=9 Hz), 4.13 (t, 2H, J=6 Hz), 2.91 (t, 2H, J=7 Hz), 2.88 (m, 2H), 2.63 (t, 2H, J=8 Hz), 2.56 (bs, 6H), 2.23 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H), and 1.49 (m, 2H). IR (KBr, cm^{-1}) 3083, 3026, 2938, 2859, 2764, 1612, 1574, 1502, 1466, 1259, 1176, and 999. MS

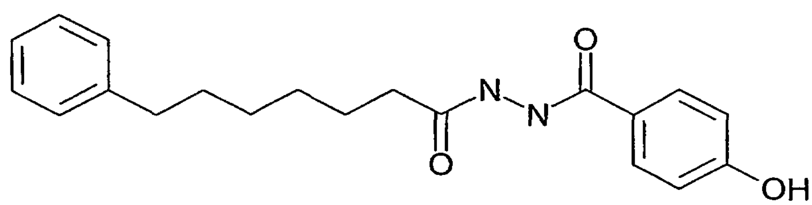
(ESI) m/e 394, 392. Anal. Calcd for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68. Found C, 72.94; H, 7.99; N, 10.52.

Example 52

Preparation of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



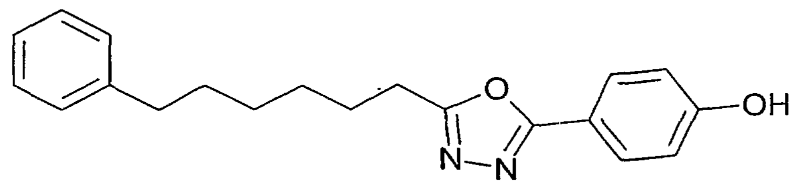
a) 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 7-phenylheptanoic acid (1.06 g, 5.0 mmol) to afford 1.39 g (81%) of 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide as a white solid (MP 154-158 °C, MW 340.43).

^{1}H NMR (DMSO-d_6) δ 10.04 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 7.72 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=7 Hz), 7.15 (m, 3H), 6.79 (d, 2H, J=9 Hz), 2.55 (t, 2H, J=8 Hz), 2.13 (t, 2H, J=8 Hz), 1.53 (m, 4H) and 1.29 (m, 4H). IR (KBr, cm^{-1}) 3213, 3024, 2931, 2855, 1765, 1684, 1670, 1646, 1610, 1583, 1506, 1492, 1464, 1453, 1308, 1279, 1254, 1225, 1174, and 699. MS (ESI) m/e 341, 339. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found C, 69.87; H, 7.05; N, 8.00.

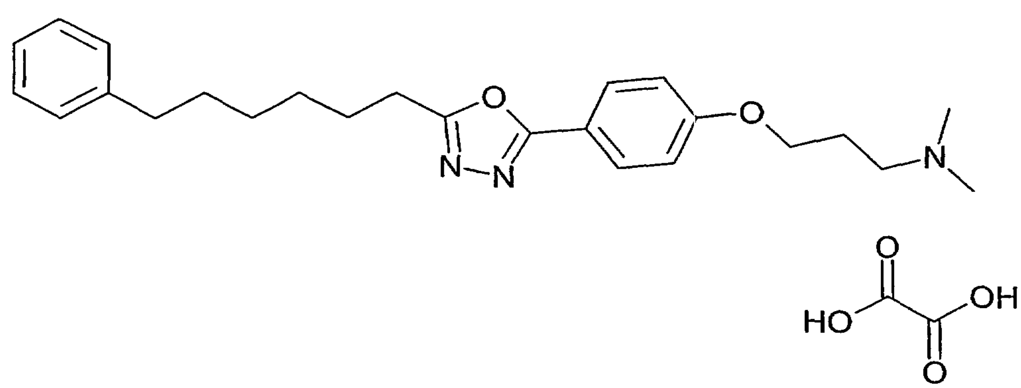
b) 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(7-phenylheptanoyl)-hydrazide (1.3 g, 3.82 mmol), triphenylphosphine (2.02 g, 7.64 mmol), and triethylamine (1.92 mL, 13.75 mmol) to afford 0.883 g (71%) of 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 125-129 °C, MW 322.41).

^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=8 Hz), 2.90 (t, 2H, J=7 Hz), 2.60 (t, 2H, J=8 Hz), 1.84 (m, 2H), 1.64 (m, 2H), and 1.43 (m, 4H). IR (KBr, cm^{-1}) 3061, 3020, 2925, 2852, 2809, 2686, 2608, 2481, 1612, 1600, 1577, 1498, 1466, 1375, 1286, 1239, and 1174. MS (ESI) m/e 323, 321. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found C, 74.27; H, 6.76; N, 8.61.

c) Dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



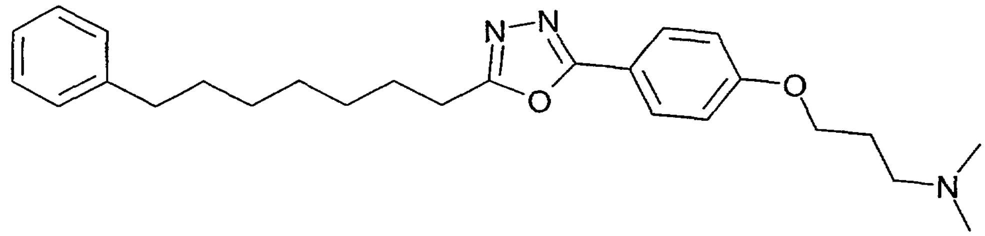
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.161 g, 0.5 mmol) to afford 0.153 g (75%) of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an oily gum. The gum (0.151 g, 0.37 mmol) was dissolved in 2 mL acetone, and oxalic acid (0.037 g, 0.41 mmol), dissolved in 1 mL acetone, was added with rapid stirring at room temperature. Filtered the resultant thick precipitate, washed the collected solid with acetone and diethyl ether, and dried in

vacuo at 40 °C to afford 0.18 g (97%) of dimethyl-(3-{4-[5-(6-phenylhexyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt as a white solid (MP 147-152 °C, MW oxalate salt 497.60, MW free amine 407.56).

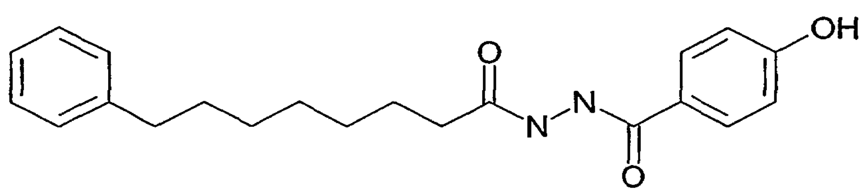
^{1}H NMR (DMSO-d_6) δ 7.90 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=7 Hz), 7.15 (m, 3H), 7.11 (d, 2H, J=9 Hz), 4.12 (t, 2H, J=6 Hz), 3.13 (t, 2H, J=7 Hz), 2.87 (t, 2H, J=7 Hz), 2.74 (s, 6H), 2.54 (t, 2H, J=8 Hz), 2.08 (m, 2H), 1.72 (m, 2H), 1.55 (m, 2H), and 1.34 (m, 4H). IR (KBr, cm^{-1}) 2970, 2925, 2854, 2676, 1721, 1612, 1590, 1496, 1311, 1232, 1177, 1040, and 842. MS (ESI) m/e 408, 408.5. Anal. Calcd for $C_{25}H_{33}N_3O_2 \cdot C_2H_2O_4$: C, 65.17; H, 7.09; N, 8.44. Found C, 64.95; H, 6.94; N, 8.39.

Example 53

Preparation of dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



a) 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide

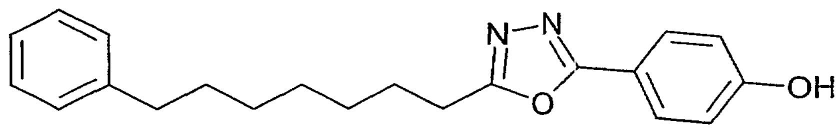


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51aa, from 8-phenyloctanoic acid (1.14 g, 5.0 mmol) to afford 1.27 g (71%) of 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide as a white solid (MP 150-152 °C, MW 354.45).

^{1}H NMR (DMSO-d_6) δ 10.04 (s, 1H), 9.97 (s, 1H), 9.68 (s, 1H), 7.72 (d, 2H, J=9 Hz), 7.24 (t, 2H, J=7 Hz), 7.15 (m, 3H), 6.79 (d, 2H, J=9 Hz), 2.55 (t, 2H, J=8 Hz), 2.13 (t, 2H, J=8 Hz), 1.53 (m, 4H) and 1.28 (bs, 6H). IR (KBr, cm^{-1}) 3280, 3023, 2927, 2852, 1759, 1659, 1607, 1575, 1515, 1494, 1277, 1237, 1181, 845, and 698. MS (ESI) m/e 355,

353. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found C, 70.45; H, 7.34; N, 7.69.

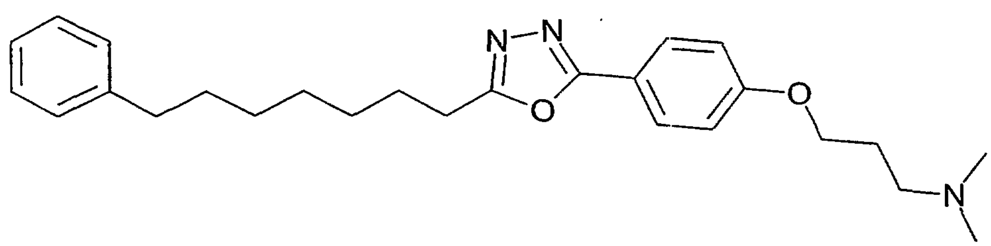
b) 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(8-phenyloctanoyl)-hydrazide (1.2 g, 3.4 mmol), triphenylphosphine (1.8 g, 6.8 mmol), and triethylamine (1.71 mL, 12.24 mmol) to afford 0.935 g (82%) of 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 138-140 °C, MW 336.44).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 7.17 (m, 3H), 6.99 (d, 2H, J=9 Hz), 2.90 (t, 2H, J=8 Hz), 2.59 (t, 2H, J=8 Hz), 1.82 (m, 2H), 1.61 (m, 2H), and 1.37 (m, 6H). IR (KBr, cm^{-1}) 3083, 3063, 3024, 2925, 2852, 1611, 1599, 1576, 1497, 1467, 1454, 1287, 1234, 1174, 862, 819, 739, and 695. MS (ESI) m/e 337, 335. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found C, 74.90; H, 7.05; N, 8.36.

c) Dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



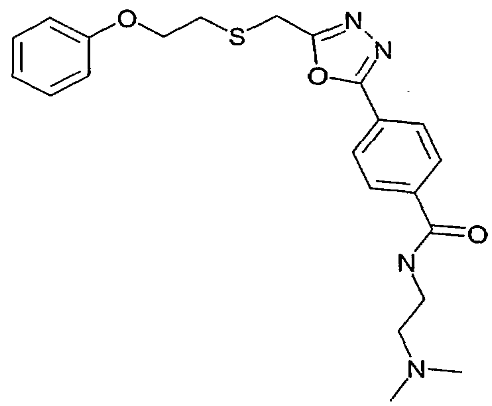
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, using 4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.168 g, 0.5 mmol) to afford 0.198 g (94%) of dimethyl-(3-{4-[5-(7-phenylheptyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as an off-white solid (MP 36-39 °C, MW 421.59).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=7 Hz), 7.17 (m, 3H), 6.98 (d, 2H, J=9 Hz), 4.12 (t, 2H, J=6 Hz), 2.89 (t, 2H, J=8 Hz), 2.74 (m, 2H), 2.59 (t, 2H, J=8

Hz), 2.48 (bs, 6H), 2.16 (m, 2H), 1.81 (m, 2H), 1.62 (m, 2H), and 1.37 (m, 6H). IR (KBr, cm^{-1}) 2925, 2853, 2765, 1613, 1500, 1468, 1254, 1174, and 836. MS (ESI) m/e 420, 422. Anal. Calcd for $C_{26}H_{35}N_3O_2$: C, 74.07; H, 8.37; N, 9.97. Found C, 73.88; H, 8.44; N, 9.90.

Example 54

Preparation of N-(2-dimethylaminoethyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

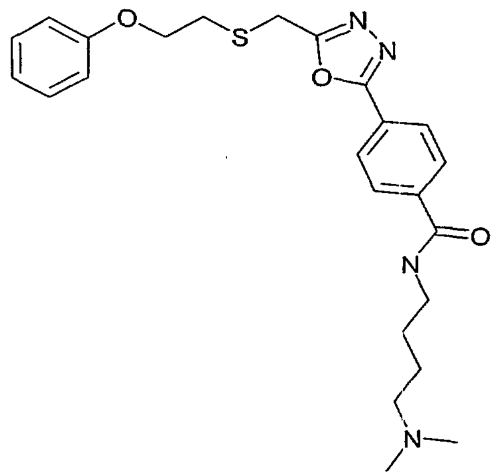


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 2-(dimethylamino)ethylamine (0.069 mL, 0.6 mmol) to afford 0.128 g (60%) of N-(2-dimethylaminoethyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as a white solid (MP 94-100 °C, MW 426.54).

^{1}H NMR ($CDCl_3$) δ 8.15 (t, 1H, J=7 Hz), 8.12 (s, 4H), 7.27 (t, 2H, J=8 Hz), 6.95 (t, 1H, J=7 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.08 (s, 2H), 3.79 (m, 2H), 3.07 (t, 2H, J=6 Hz), 2.99 (m, 2H), and 2.67 (bs, 6H). IR (KBr, cm^{-1}) 3350, 2943, 2819, 2766, 1643, 1554, 1538, 1494, 1245, 1033, 863, and 750. MS (ESI) m/e 427, 425. Anal. Calcd for $C_{22}H_{26}N_4O_3S$: C, 61.95; H, 6.14; N, 13.14; S, 7.52. Found C, 61.40; H, 5.90; N, 13.00; S, 7.59. Analytical HPLC: 97% purity.

Example 55

Preparation of N-(4-dimethylaminobutyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

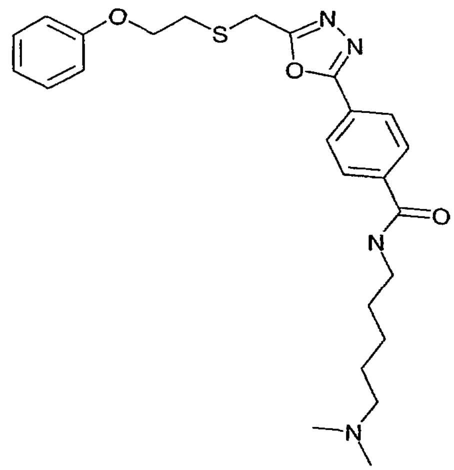


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'-carbonyldiimidazole (0.082 g, 0.505 mmol), and 4-(dimethylamino)butylamine (0.07 g, 0.6 mmol) to afford 0.136 g (60%) of N-(4-dimethylaminobutyl)-4-[5-(2- phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white waxy solid (MP 71-78 °C, MW 454.60).

^{1}H NMR ($CDCl_3$) δ 8.11 (bs, 1H), 8.09 (d, 2H, J=9 Hz), 8.05 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 6.95 (t, 1H, J=7 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.53 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.78 (m, 2H), 2.56 (bs, 6H), and 1.83 (m, 4H). IR (KBr, cm^{-1}) 3338, 2943, 1643, 1602, 1554, 1533, 1494, 1468, 1289, 1246, 749, and 691. MS (ESI) m/e 453, 455. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65; N, 12.32; S, 7.05. Found C, 62.75; H, 6.77; N, 12.53; S, 6.93. Analytical HPLC: 97% purity.

Example 56

Preparation of N-(5-dimethylaminopentyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

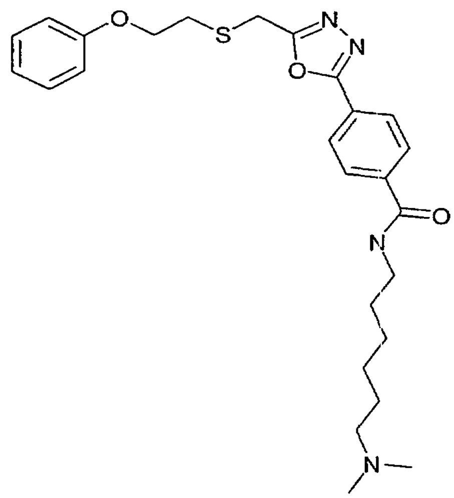


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'- carbonyldiimidazole (0.082 g, 0.505 mmol), and 5-(dimethylamino)pentylamine (0.078 g, 0.6 mmol) to afford 0.126 g (53%) of N-(5-dimethylaminopentyl)-4-[5-(2- phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white waxy solid (MP 83-89 °C, MW 468.62).

^{1}H NMR ($CDCl_3$) δ 8.11 (bs, 1H), 8.09 (d, 2H, J=8 Hz), 7.98 (d, 2H, J=8 Hz), 7.27 (m, 2H), 6.93 (t, 1H, J=7 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.52 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.62 (m, 2H), 2.48 (bs, 6H), 1.71 (m, 4H), and 1.54 (m, 2H). IR (KBr, cm^{-1}) 3346, 2942, 2761, 1717, 1644, 1554, 1533, and 1246. MS (ESI) m/e 467, 469. Anal. Calcd for $C_{25}H_{32}N_4O_3S$: C, 64.08; H, 6.88; N, 11.96; S, 6.84. Found C, 63.05; H, 6.78; N, 11.71; S, 6.47. Analytical HPLC: 96% purity.

Example 57

Preparation of N-(6-dimethylaminohexyl)-4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

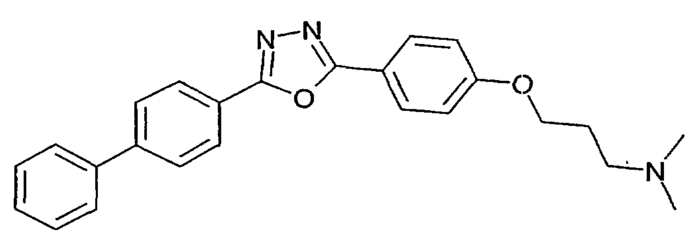


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 47f, from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.178 g, 0.5 mmol), 1,1'- carbonyldiimidazole (0.082 g, 0.505 mmol), and 6-(dimethylamino)hexylamine (0.087 g, 0.6 mmol) to afford 0.148 g (61%) of N-(6-dimethylaminohexyl)-4-[5-(2- phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide as an off-white solid (MP 86-93 °C, MW 482.65).

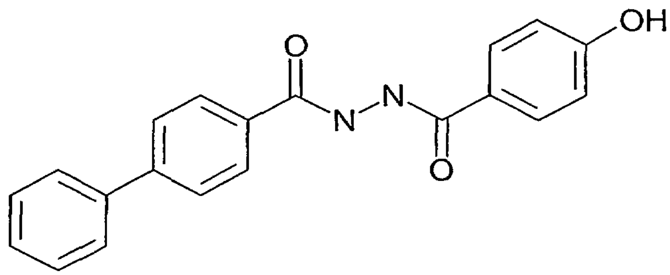
^{1}H NMR ($CDCl_3$) δ 8.13 (bs, 1H), 8.10 (d, 2H, J=9 Hz), 8.02 (d, 2H, J=9 Hz), 7.27 (t, 2H, J=8 Hz), 6.95 (t, 1H, J=8 Hz), 6.89 (d, 2H, J=8 Hz), 4.22 (t, 2H, J=6 Hz), 4.07 (s, 2H), 3.51 (m, 2H), 3.06 (t, 2H, J=6 Hz), 2.87 (m, 2H), 2.70 (bs, 6H), 1.83 (m, 2H), 1.71 (m, 2H) and 1.47 (m, 4H). IR (KBr, cm^{-1}) 3339, 2929, 2854, 2815, 2776, 1642, 1602, 1580, 1554, 1532, 1492, 1468, 1247, 1017, 749, and 691. MS (ESI) m/e 481, 483. Anal. Calcd for $C_{26}H_{34}N_4O_3S$: C, 64.70; H, 7.10; N, 11.61; S, 6.64. Found C, 63.86; H, 7.13; N, 12.19; S, 6.76. Analytical HPLC: 97% purity.

Example 58

Preparation of {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine



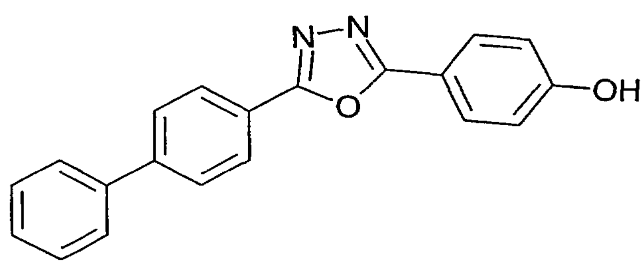
a) 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 4-biphenylcarboxylic acid (1.04 g, 5.0 mmol) to afford 1.52 g (91%) of 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide as an off-white solid (MP 279-281 °C, MW 332.36).

^{1}H NMR (DMSO-d_6) δ 10.44 (s, 1H), 10.24 (s, 1H), 10.09 (s, 1H), 8.00 (d, 2H, J=9 Hz), 7.81 (d, 2H, J=8 Hz), 7.79 (d, 2H, J=9 Hz), 7.74 (d, 2H, J=8 Hz), 7.49 (t, 2H, J=8 Hz), 7.40 (t, 1H, J=7 Hz), and 6.84 (d, 2H, J=9 Hz). IR (KBr, cm^{-1}) 3272, 1674, 1622, 1608, 1582, 1513, 1492, 1484, 1284, 1277, 1236, 847, and 745. MS (ESI) m/e 331, 333. Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found C, 72.52; H, 4.99; N, 8.27.

b) 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2- yl)-phenol

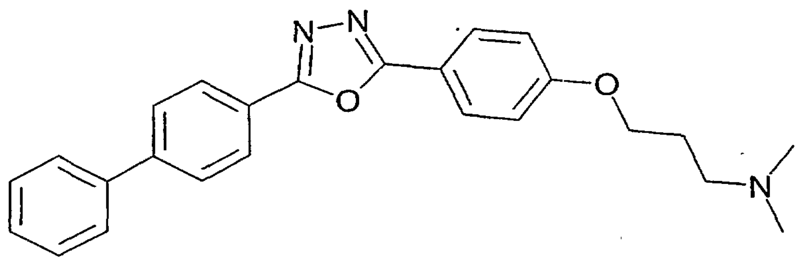


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(biphenyl-4-carbonyl)-hydrazide (1.33 g, 4.0 mmol), triphenylphosphine (2.12 g, 8.0 mmol), and triethylamine (2.0 mL, 14.4 mmol) to afford 0.343 g (27%) of 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenol as an off-white solid (MP 256-260 °C, MW 314.35).

^{1}H NMR (DMSO-d_6) δ 10.34 (s, 1H), 8.17 (d, 2H, J=8 Hz), 7.97 (d, 2H, J=8 Hz), 7.92 (d, 2H, J=8 Hz), 7.77 (d, 2H, J=8 Hz), 7.51 (t, 2H, J=8 Hz), 7.42 (t, 1H, J=8 Hz), and 6.97 (d, 2H, J=8 Hz). IR (KBr, cm^{-1}) 3110, 1613, 1498, 1483, 1293, 1176, 1074, 838, and

739. MS (ESI) m/e 313, 315. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found C, 76.34; H, 4.75; N, 8.35.

c) {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine

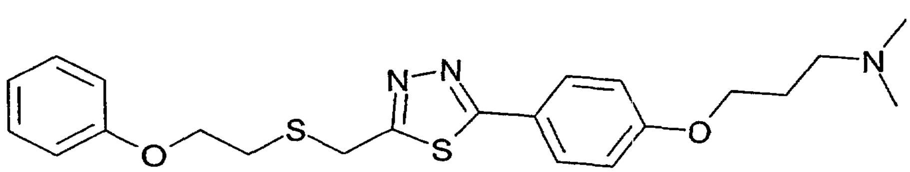


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenol (0.157 g, 0.5 mmol) to afford 0.162 g (81%) of {3-[4-(5-biphenyl-4-yl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethylamine as a white solid (MP 130-132 °C, MW 399.50).

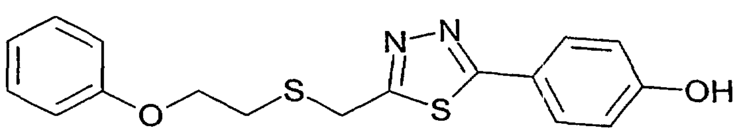
^{1}H NMR ($CDCl_3$) δ8.19 (d, 2H, J=9 Hz), 8.09 (d, 2H, J=9 Hz), 7.76 (d, 2H, J=9 Hz), 7.66 (d, 2H, J=8 Hz), 7.49 (t, 2H, J=7 Hz), 7.41 (t, 1H, J=7 Hz), 7.03 (d, 2H, J=8 Hz), 4.18 (t, 2H, J=6 Hz), 3.07 (m, 2H), 2.72 (bs, 6H), and 2.36 (m, 2H). IR (KBr, cm^{-1}) 2940, 2752, 1613, 1473, 1464, 1257, 1006, 842, and 740. MS (ESI) m/e 400. Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found C, 73.89; H, 6.33; N, 10.35. Analytical HPLC: 95% purity.

Example 59

Preparation of Dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine



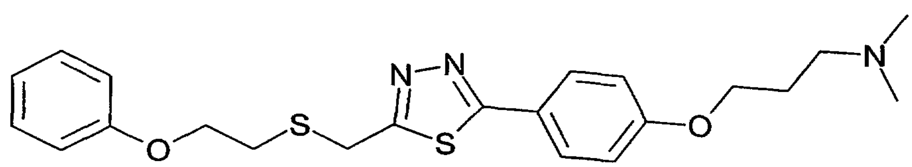
a) 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol



A heterogeneous mixture of 4-hydroxy-benzoic acid N'-[2-(2-phenoxyethylsulfanyl)-acetyl]-hydrazide (1.04 g, 3.0 mmol), and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent) (1.25 g, 3.0 mmol) in 30 mL toluene was stirred at reflux temperature (111 °C) for 1.5 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to afford 2.37 g of a yellow solid. Purification by column chromatography on silica gel (elution with linear gradient of 0-100% ethyl acetate/hexane followed by isocratic elution with 5% methanol/ethyl acetate) afforded 0.144 g (14%) of 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol as a white solid (MP 127-128 °C, MW 344.46).

^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.76 (d, 2H, J=9 Hz), 7.25 (t, 2H, J=8 Hz), 6.90 (m, 5H), 4.32 (s, 2H), 4.14 (t, 2H, J=6 Hz), and 2.93 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3415, 3125, 2920, 1600, 1586, 1496, 1243, 1177, 1032, 754, and 690. MS (ESI) m/e 345, 343. Anal. Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13; S, 18.62. Found C, 59.24; H, 4.71; N, 8.20; S, 18.36.

b) Dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine

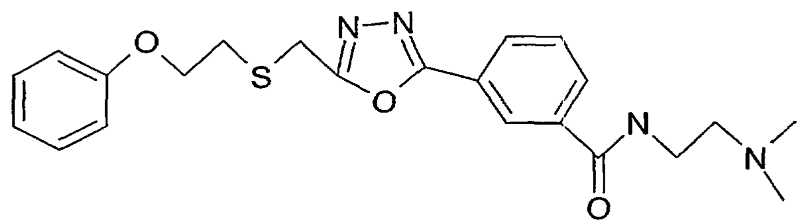


The above compound was prepared as exemplified in Example 50f, using 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenol (0.12 g, 0.35 mmol) to afford 0.038 g (25%) of dimethyl-(3-{4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]thiadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 72-73 °C, MW 429.61).

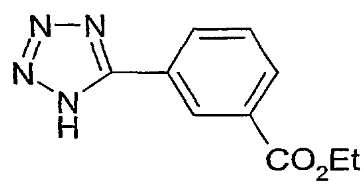
^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=8 Hz), 6.95 (d, 2H, J=9 Hz), 6.91 (t, 1H, J=8 Hz), 6.88 (d, 2H, J=8 Hz), 4.22 (s, 2H), 4.18 (m, 4H), 3.25 (m, 2H), 2.99 (t, 2H, J=6 Hz), 2.87 (s, 3H), 2.86 (s, 3H), and 2.47 (m, 2H). IR (KBr, cm^{-1}) 2948, 2923, 2873, 2825, 2779, 1602, 1499, 1465, 1452, 1253, 1178, 1057, 955, 842, and 757. MS (ESI) m/e 428, 430. Anal. Calcd for $C_{22}H_{27}N_3O_2S_2$: C, 61.51; H, 6.33; N, 9.78; S, 14.93. Found C, 61.89; H, 6.68; N, 9.19; S, 13.88. Analytical HPLC: 91% purity.

Example 60

Preparation of *N*-(2-Dimethylamino-ethyl)3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



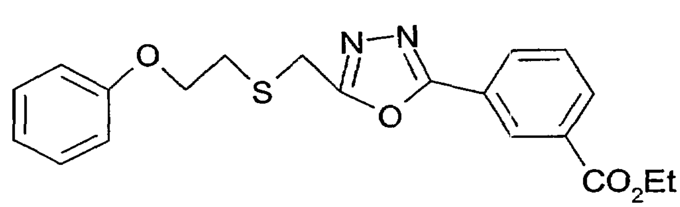
a) 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester



A solution of 3-cyano-benzoic acid ethyl ester (2.00 g, 11.4 mmol), sodium azide (2.22 g, 34. 2 mmol), and triethylamine hydrochloride (4.71 g, 34.2 mmol) in 40 mL toluene was heated to 100°C for 4.5 h. The mixture was cooled to room temperature and 150 mL of H_2O was added. The suspension was stirred for 10 min. and transferred to a separatory funnel and separated. The aqueous layer was transferred to a round-bottom flask with H_2O (50 mL), cooled to 0°C and acidified with HCl (conc). The resultant precipitate was collected by filtration, washed with H_2O, and dried in vacuo to afford 2.36 g (95%) of 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester as a white solid.

^{1}H NMR (DMSO-d6) δ 8.62 (s, 1H), 8.30 (d, 1H, J= 8 Hz), 8.13 (d, 1H, J=8 Hz), 7.76 (t, 1H, J=8 Hz), 4.36 (q. 2H, J=7 Hz) and 1.3 (t, 3H, J=7 Hz). IR (KBr, cm^{-1}) 3153, 3102, 2924, 1690, 1295, 1277, and 733. MS (ESI) m/e 217. Anal. Calcd for $C_{10}H_{10}N_4O_2Cl$: C, 55.04; H, 4.62; N, 25.67. Found C, 55.09; H, 4.64; N, 25.39.

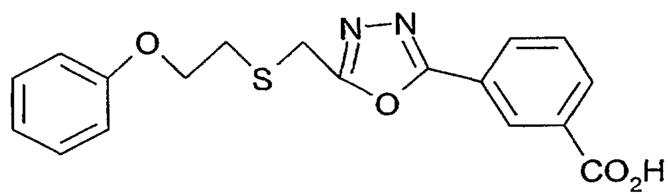
b) 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl ester



To a solution of thiolacetic acid (0.65 g, 3.1 mmol) and 1,3-dicyclohexylocarbodiimide (0.64 g, 3.1 mmol) in 5 mL of toluene was added 3-(1*H*-Tetrazol-5-yl)-benzoic acid ethyl ester (0.67 g, 3.1 mmol). The reaction mixture was heated to 111°C for 20 min., concentrated *in vacuo* and titurated with CH_2Cl_2 (5 mL). The resultant precipitate was collected by filtration and the filtrate concentrated *in vacuo*. The filtrate was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate and toluene) to afford 0.880 g (75%) of 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl ester .

^1H NMR ($CDCl_3$) δ 8.7 (s, 1H,), 8.2 (m, 2H), 7.6 (t, 1H, J=8 Hz), 7.3 (m, 3H), 6.9 (m, 2H), 4.4 (q, 2H, J=7 Hz), 4.2 (t, 2H, 6 Hz), 4.086 (s, 2H), 3.1 (t, 2H, J=6 Hz), and 1.4 (t, 3H, J=7Hz). IR (KBr, cm^{-1}) 2935, 1719, 1601, 1498, 1303, 1244. MS (ESI) m/e 385. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found C, 61.7; H, 5.34; N, 6.83.

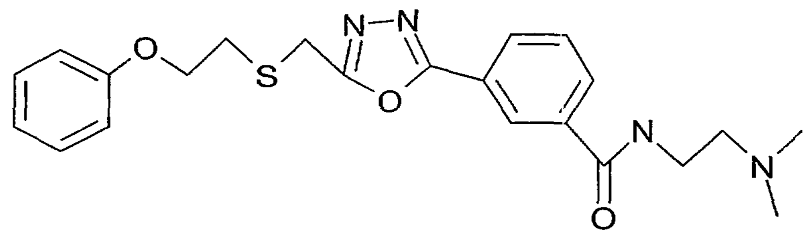
c) 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



A solution of 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid ethyl ester (0.880 g, 2.29 mmol) and lithium hydroxide (0.164 g, 6.87 mmol) in water (3 mL) and THF (7 mL) was stirred at room temperature overnight. Concentrated HCl (0.59 mL) was added and the resulting precipitate was collected by filtration and dried *in vacuo* to afford 0.694 g (85%) of 3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid as a gold solid.

^1H NMR (DMSO-d6) δ 8.5 (s, 1H), 8.1 (m, 2H), 7.7 (t, 1H, J=7.7 Hz), 7.25 (m, 2H), 6.9 (m, 3H), 4.2 (s, 2H), 4.2 (t, 2H, J=6.2 Hz), and 3.0 (t, 2H, J=6.3 Hz). IR (KBr, cm^{-1}) 3419, 3295, 2928, 2852, 1717, 1600, 1498, 1246, 757, 714, and 690. MS (ESI) m/e 357, 355. Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found C, 58.25; H, 5.16; N, 6.99.

d) N-(2-Dimethylamino-ethyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

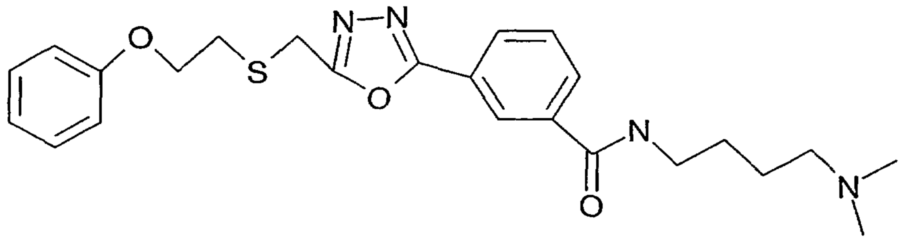


3-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid was added to a nitrogen flushed vessal with CH_2Cl_2 (5 mL) followed by the addition of oxalyl chloride (0.397 g, 3.13 mmol) and DMF (2 drops). The mixture was stirred at room temperature for 35 min., concentrated in *vacuo* and azeotroped with CH_2Cl_2 (3 X 5 mL) to give 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoyl chloride. N1,N1-Dimethyl-ethane-1,2-diamine was dissolved in CH_2Cl_2 (1 mL) and added to a nitrogen flushed vessal. 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoyl chloride was dissolved in CH_2Cl_2 (3 mL) and added dropwise. The reaction was stirred at room temperature overnight and diluted with water, CH_2Cl_2, and NaOH (1N). The aqueous layer was extracted 2 times with CH_2Cl_2. The combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with 95 $CHCl_3$/5 NH_3 (2.0M in MeOH) to afford 0.167 g (63%) of N-(2-dimethylamino-ethyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide. Recrystallization from Et_2O and EtOAc gave 0.079 g (30%) of the title compound.

^{1}H NMR (DMSO-d6) δ 8.7 (t, 1H, J=5 Hz), 8.4 (s, 1H), 8.1 (m, 2H), 7.7 (t, 1H, J=8), 7.2 (m, 2H), 6.9 (m, 3H), 4.2 (s, 2H), 4.2 (t, 2H, J=6 Hz), 3.4 (m, 2H,), 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.1 (s, 6H). IR (KBr, cm^{-1}) 2952, 2864, 2827, 2785, 1658, 1601, 1498, 1243. MS (ESI) m/e 428, 429, 425. Anal. Calcd for $C_{22}H_{26}N_4O_3S$: C, 61.95; H, 6.14; N, 13.14. Found C, 61.80; H, 6.23; N, 12.92. MP=64°C.

Example 61

Preparation of N-(4-dimethylamino-butyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

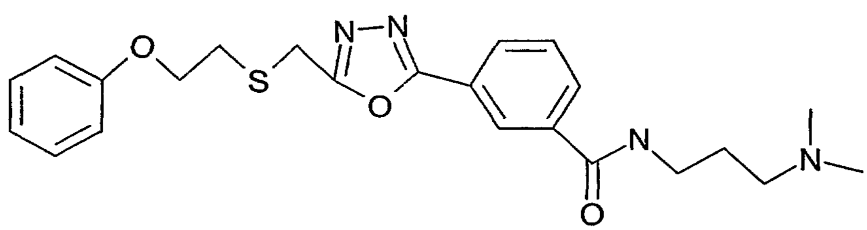


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60, from 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.353 g, 1.0 mmol) and N1,N1-dimethyl-butane-1,4-diamine (0.230 g, 1.98 mmol) to give 0.346 g (77%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 8.4 (s, 1H), 8.1, (d, 1H, J=8 Hz), 8.0 (d, 1H, J=8 Hz), 7.6, (t, 1H, J=8 Hz), 7.2 (m, 3H), 6.9 (m, 2H), 4.2 (t, 2H, J=6 Hz), 4.1 (s, 2H), 3.5 (q, 2H, J=5 Hz), 3.1 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=6 Hz), 2.2 (s, 6H), 1.8 (m, 2H), 1.7 (m, 2H). IR (KBr, cm^{-1}) 2940, 2864, 2826, 2784, 1659, 1601, 1549, 1498, 1243. MS (ESI) m/e 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65; N, 12.32. Found C, 63.52; H, 7.17; N, 12.07. MP=38-42°C.

Example 62

Preparation of N-(3-dimethylamino-propyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



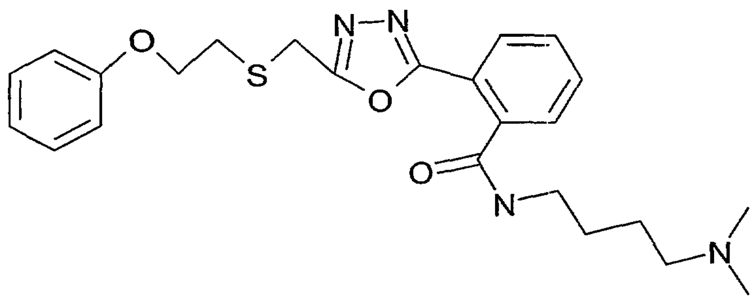
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60, from 3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.387 g, 1.1 mmol) and N1,N1-dimethyl-propane-1,3-diamine (221 mg, 2.16.mmol) to give 0.046 g (10%) of N-(3-dimethylamino-propyl)-3-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide.

^{1}H NMR ($CDCl_3$) δ 9.1 (s, br, 1H), 8.4, (s, 1H), 8.14 (d, 1H, J=8 Hz), 8.1 (d, 1H, J=8 Hz), 7.3 (m, 2H), 6.94 (t, 1H, J=7 Hz), 6.9 (d, 2H, J=8 Hz) 4.2 (t, 2H, J=6 Hz), 4.1 (s, 2H), 3.6 (m, 2H), 3.1)t, 2H, J=6 Hz), 2.6 (m, 2H), 2.4 (s, 6H), 1.8 (q, 2H, J=6 Hz). IR

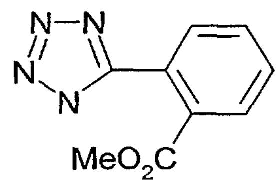
(KBr, cm^{-1}) 3018, 1653, 1548, 1498, 1243. MS (ESI) m/e 441, 439. HPLC 100%. Anal. Calcd for $C_{23}H_{28}N_4O_3S$: C, 62.70; H, 6.41; N, 12.72. Found C, 61.60; H, 6.19; N, 12.22. MP=88-90°C.

Example 63

Preparation of N-(4-dimethylamino-butyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



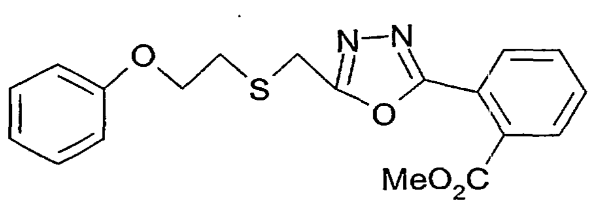
a) 2-(1H-Tetrazol-5-yl)-benzoic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60a, from 2-cyano-benzoic acid methyl ester (2.031g, 12.6 mmol) to give 1.87g (73%) of 2-(1H-tetrazol-5-yl)-benzoic acid methyl ester.

^{1}H NMR (DMSO-d6) δ 7.9 (m, 1H), 7.7 (m, 3H), 3.7 (s, 3H). IR (KBr, cm^{-1}) 1715, 1273. MS (ESI) m/e 203. Anal. Calcd for $C_9H_8N_4O_2$: C, 55.04; H, 4.62; N, 25.67. Found C, 53.68; H, 3.89; N, 28.61.

b) 2-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester

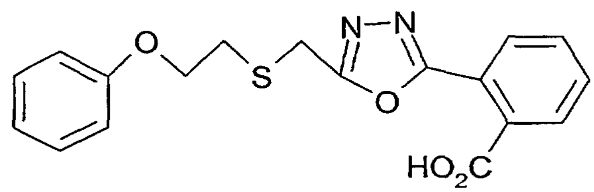


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60b, from 2-(1H-Tetrazol-5-yl)-benzoic acid methyl ester (0.705

g, 3.45 mmol) to give 0.985 g (73%) of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester.

^{1}H NMR ($CDCl_3$) δ 7.9 (m, 1H), 7.8 (m, 1H), 7.6 (m, 1H), 7.2 (m, 2H), 6.95 (t, 1H, J=7 Hz), 6.9 (d,2H, J=9 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (s, 2H), 3.8 (s, 3H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 1728, 1601, 1498, 1299, 1276, 1243. MS (ESI) m/e 371. Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found C, 61.41; H, 4.94; N, 7.46.

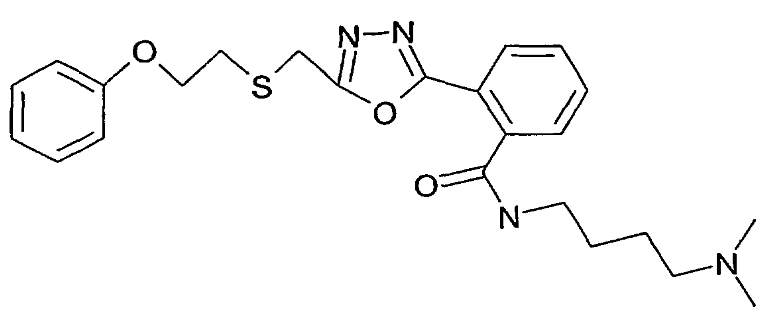
c) 2-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60c, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (0.929 g, 2.51 mmol) with the exception that a gold oil formed upon treatment with conc. HCl. This material was titurated with H_20 and concentrated to dryness in vacuo to give 0.808 g (90%) of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid.

^{1}H NMR (CD_3OD) δ 8.1 (m, 1H), 7.7 (m, 3H), 7.2 (m, 2H), 6.9 (m, 3H), 4.2 (t, 2H, J=6 Hz) 4.16 (s, 2H), 3.1 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3430, 1723, 1635, 1601, 1241. MS (ESI) m/e 357, 355. Anal. Calcd for $C_8H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found C, 55.74; H, 4.48; N, 7.28.

d) N-(4-Dimethylamino-butyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

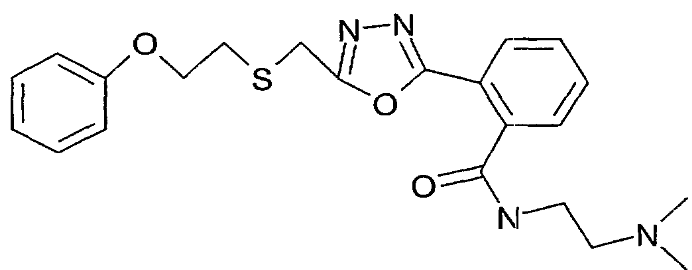


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60d, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.434 g, 1.22 mmol) and N1,N1-dimethyl-butane-1,4-diamine (0.283 g, 2.44.mmol) to give 0.334 g (60%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 8.1 (s (br), 1H), 7.9 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.3 (m, 2H), 6.95 (t, 1H, J=6 Hz), 6.9 (d, 2H, J=8 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (s, 2H), 3.4 (q, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.3 (t, 2H, J=6 Hz), 2.0 (s, 6H), 1.66 (m, 2H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 3008, 2941, 2864, 2824, 2782, 1721, 1662, 1601, 1588, 1498, 1469, 1243. MS (ESI) m/e 455, 453. Anal. Calcd for $C_{24}H_{30}N_4O_3S$: C, 63.41; H, 6.65; N, 12.32. Found C, 63.38; H, 7.01; N, 11.73. MP = 62-65°C.

Example 64

Preparation of N-(2-dimethylamino-ethyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

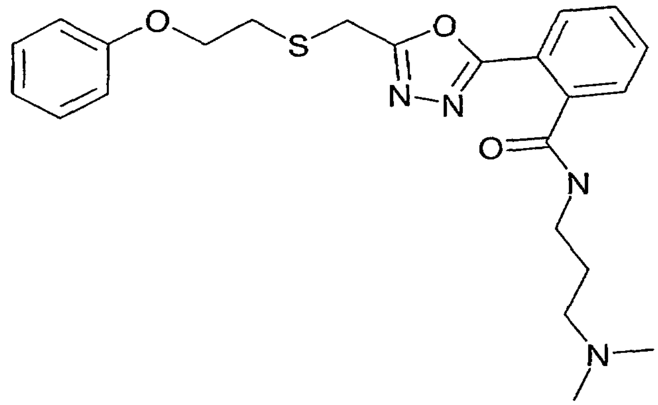


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 60d, from 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.169g, 0.474 mmol) and N1,N1-dimethyl-ethane-1,2-diamine (0.084 g, 0.948 mmol) to give 0.082 g (41%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 7.8 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.2 (m, 2H), 6.9 (t, 1H, J=7 Hz), 6.8 (d, 2H, J=8 Hz), 4.1 (t, 2H, J=6 Hz), 3.9 (s, 2H), 3.5 (m, 2H), 3.0 (t, J=6 Hz) 2.5 (s, br, 1H), 2.2 (s, 6H). IR (KBr, cm^{-1}) 3009, 1722, 1665, 1601, 1498, 1470, 1402, 1242. MS (ESI) m/e 427, 425. Anal. Calcd for $C_{22}H_{26}N_4O_3S$: C, 61.95; H, 6.14; N, 13.13. Found C, 59.49; H, 5.91; N, 12.18. MP=80-85°C.

Example 65

Preparation of N-(3-dimethylamino-propyl)-2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzamide

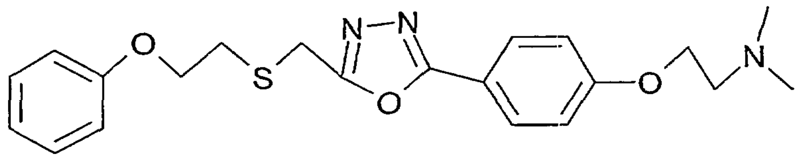


To a solution of 2-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (0.159 g, 0.45 mmol) in 3 mL THF was added 1,1'-carbonyldiimidazole (0.073 g, 0.45mM) and 0.044 mL DMF. The mixture was heated to 60°C for 30 min followed by stirring at room temperature for 5 min. N1,N1-Dimethyl-propane-1,3-diamine (0.091 g, 0.89 mmol) was added to the mixture and stirring was continued at room temperature for 2 hours. The mixture was extracted with ethyl acetate and washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography on silica gel (elution with chloroform and 2M ammonia in methanol gave 0.072 g (37%) of the title compound.

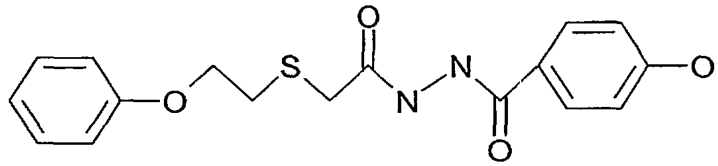
^{1}H NMR ($CDCl_3$) δ 7.9 (d, 1H, J=7 Hz), 7.5 (m, 3H), 7.3 (m, 2H), 7.1 (s, 1H), 6.96 (t, 1H, J=7 Hz), 6.9 (d, 3H, J=9 Hz), 4,2 (7, 2H, J=6 Hz), 4.0 (s, 2H), 3.5 (m, 2H), 3.0 (t, 2H, J=6 Hz), 2.5 (t, 2H, J=6 Hz), 2.2 (s, 6H), 1.7 (m, 2H, J=6 Hz). IR (KBr, cm^{-1}) 2928, 2864, 1722, 1684, 1498, 1242. MS (ESI) m/e 441. Anal. Calcd for $C_{23}H_{28}N_4O_3S$: C, 62.70; H, 6.41; N, 12.72. Found C, 58.41; H, 6.16; N, 11.47. MP=60-65°C.

Example 66

Preparation of dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



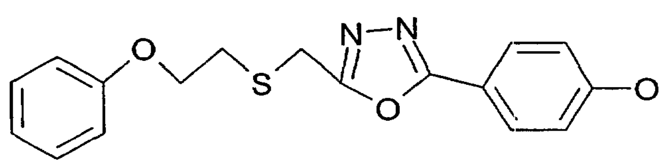
a) 4-Hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



A solution of (2-phenoxy-ethylsulfanyl)-acetic acid (0.848 g, 4.0 mmol) and (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate), (EEDQ), (0.989 g, 4.0 mmol) in 20 mL acetonitrile and 5 mL THF were stirred together at room temperature for 1 hr. 4-Hydroxy-benzoic acid hydrazide (0.608 g, 4.0 mmol) was added and the mixture was sonicated for 2 hrs and stirred at room temperature for 16 hrs. The mixture was concentrated to low volume and extracted with ethyl acetate. The organic extract was washed with 1N HCl, H_2O, $NaHCO_3$, brine, dried over magnesium sulfate, filtered, and concentrated to dryness to give 1.28 g (92%) of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide.

^{1}H NMR (DMSO-d6) δ 10.2 (s, 1H), 10.1 (s, 1H), 10.0 (s, 1H), 7.7 (d, 2H, J=9 Hz), 7.3 (m, 2H), 6.9 (m, 3H), 6.8 (d, 2H, J=9 Hz), 4.2 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3305, 3201, 3003, 2918, 2867, 1696, 1623, 1609, 1584, 1517, 1287, 1242, 1229. MS (ESI) m/e 347, 345. Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.95; H, 5.24; N, 8.09. Found C, 58.37; H, 5.51; N, 7.19.

b) 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol

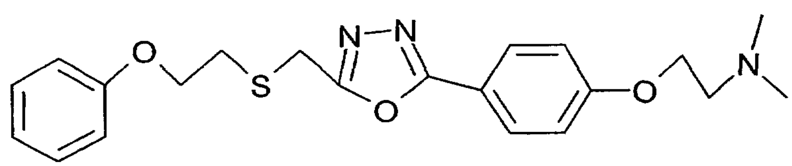


A solution of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (4.87 g, 14.1 mmol), triphenyl phosphine (7.38 g, 28.1 mmol), and

triethylamine (5.14 g, 50.7 mmol) were stirred together in acetonitrile (15 mL). Carbon tetrachloride (9.17 g, 57.9 mmol) was added and the mixture was stirred at room temperature for 3 hrs. The material was concentrated to low volume and diluted with hexane (100 mL), ethyl acetate (6 mL), and ethanol (25 mL). The mixture was sonnicated for 5 minutes and a precipitate formed. The solid was collected and dried in vaccuo (30°C). The solid was slurried with 1N HCl, collected and dried to give 3.149 g (68%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.8 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 6.9 (m, 5H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3410, 1762, 1611, 1601, 1498, 1242, 1226, 1174, 752. MS (ESI) m/e 329, 327. Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found C, 61.99; H, 5.00; N, 7.92. M.P.=172-175°C.

c) Preparation of dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



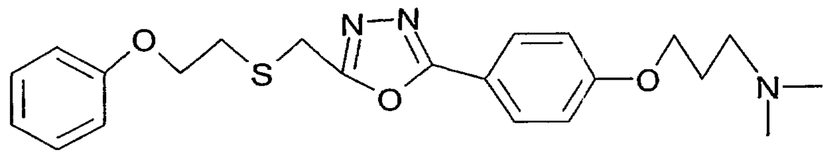
A solution of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.214 g, 0.652 mmol) and 60% NaH (0.075 g, 1.95 mmol) was stirred at 5°C in 10 mL DMF for 2 min. at which time (2-chloro-ethyl)-dimethyl-amine, hydrochloride (0.140 g, 0.978 mmol) was added and the mixture was stirred at 100°C for 2.5 hours. The resultant mixture was extracted 2 times with ethyl acetate and washed with water, brine, dried over sodium sulfate and concentrated to give 0.243 g of crude product. This was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate, toluene followed by chloroform/2M ammonia in methanol) to give a yellow oil which was recrystallized from ethyl ether and ethyl acetate to give 0.098 g (38%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=5 Hz), 2.2 (s, 6H). IR (KBr, cm^{-1}) 1616, 1499, 1466, 1253, 1242, 1177, 756. MS (ESI) m/e 400.9. Anal. Calcd for

$C_{21}H_{25}N_3O_3S$: C, 63.14; H, 6.31; N, 10.52. Found C, 62.92; H, 6.09; N, 10.38. MP=62-64°C.

Example 67

Preparation of dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

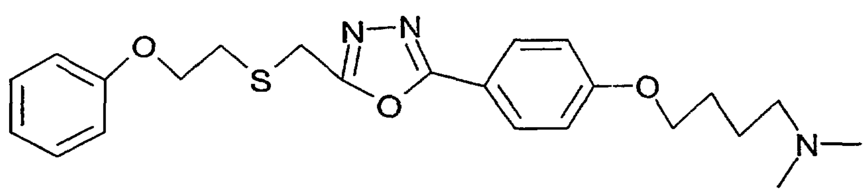


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.548 g, 1.67 mmol) and (3-chloro-propyl)-dimethyl-amine, hydrochloride (396 mg, 2.5 mmol) to give 0.288 g (42%) of the title compound.

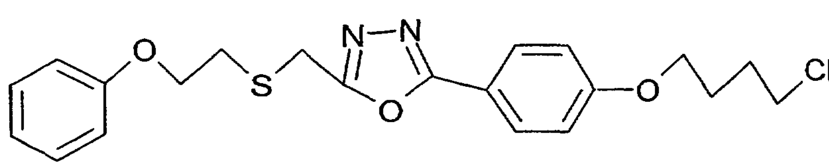
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.3 (t, 2H, J=7 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.9 (m, 2H). IR (KBr, cm^{-1}) 2934, 1612, 1601, 1503, 1491, 1466, 1253, 1243, 1178, 762. MS (ESI) m/e 414. Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found C, 63.55; H, 6.50; N, 10.04. MP=70°C.

Example 68

Preparation of dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine



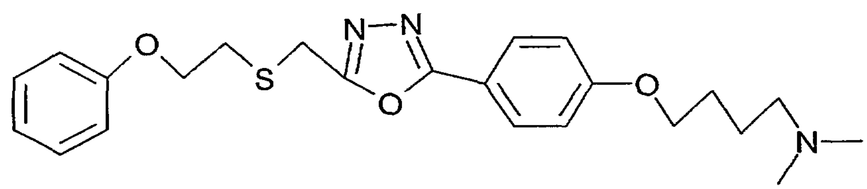
a) 2-[4-(4-Chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



A solution of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.202 g, 0.615 mmol), 1-bromo-4-chloro-butane (0.158 g, 0.922 mmol), and potassium carbonate (0.195 g, 1.41mM) was refluxed in 5 mL acetone overnight. The solid was removed by filtration and the filtrate concentrated to dryness. Recrystallization of the filtrate from ether and ethyl acetate gave 0.127 g (49%) of 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^{1}H NMR (DMSO-d6) δ 7.8 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.7 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 1.9 (m, 4H). IR (KBr, cm^{-1}) 1614, 1604, 1586, 1499, 1253, 1242, 1176. MS (ESI) m/e 419, 417. Anal. Calcd for $C_{21}H_{23}ClN_2O_3S$: C, 61.80; H, 6.09; N, 6.26. Found C, 59.82; H, 5.67; N, 6.41.

b) Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine

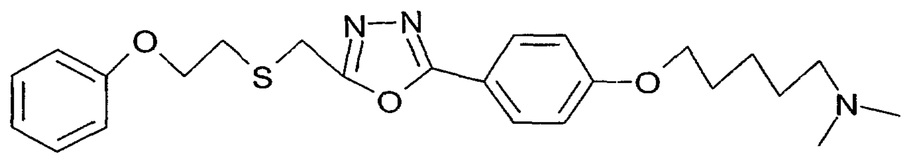


A solution of 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.127 g, 0.303 mmol), dimethyl amine (2M THF, 3.8 mL, 7.58 mmol), NaI (0.004 g, 0.0236 mmol), and $NaHCO_3$ (0.071 g, 0.84 mmol) in 4 mL DMF was heated to 80°C overnight in a sealed tube. The mixture was extracted with ethyl acetate followed by washing with water, brine, dried over sodium sulfate and concentrated to dryness. The residue was purified directly by column chromatography on silica gel (elution with ethyl acetate/ toluene followed by 90% chloroform/10% 2M ammonia in methanol) to give 0.090 g (70%) of the title compound.

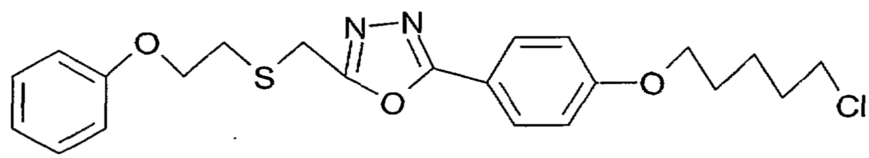
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2h, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.5 (m, 2H). IR (KBr, cm^{-1}) 2763, 1612, 1501, 1259, 1246, 1177, 999, 841. MS (ESI) m/e 428. Anal. Calcd for $C_{23}H_{29}N_3O_3S$: C, 64.61; H, 6.84; N, 9.83. Found C, 64.60; H, 6.85; N, 9.69. MP=62-63°C.

Example 69

Preparation of dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-pentyl)-amine



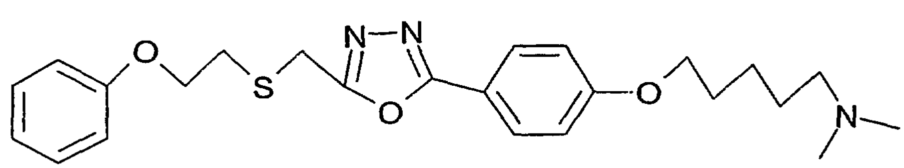
a) 2-[4-(5-Chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.304 g, 0.926 mmol), and 1-bromo-5-chloro-pentane (0.250 g, 1.38 mmol) to give 0.260 g (65%) of 2-[4-(5-chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz) 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m 4H), 4.0 (t, 2H, J=6 Hz), 3.6 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 1.8 (m, 4H), 1.5 (m, 2H). IR (KBr, cm^{-1}) 1611, 1503, 1490, 1258, 1244, 1178, 1005, 844, 765. MS (ESI) m/e 433. Anal. Calcd for $C_{22}H_{25}N_2ClO_3S$: C, 61.03; H, 5.82; N, 6.47. Found C, 59.71; H, 5.75; N, 6.34.

b) Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-pentyl)-amine

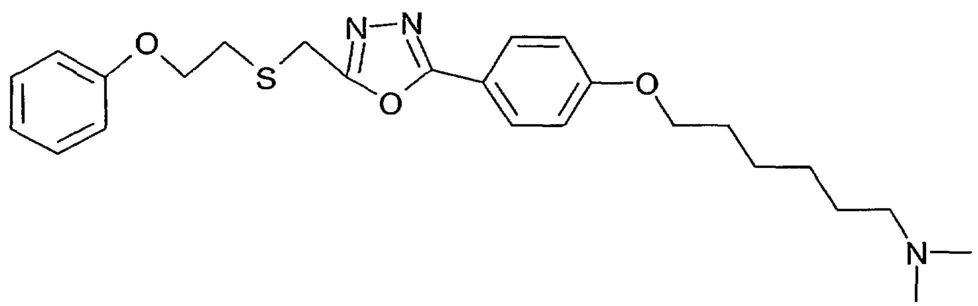


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(5-chloro-pentyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.210 g, 0.487 mmol) to give 0.111 g (52%) of the title compound.

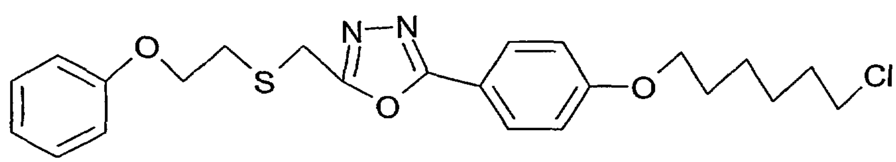
[1]H NMR (DMSO-d6) δ 7.8 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz) 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.4 (m, 4H). IR (KBr, cm^{-1}) 2941, 1602, 1610, 1500, 1466, 1253, 1175, 1032, 835, 751. MS (ESI) m/e 442. Anal. Calcd for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.51. Found C, 65.47; H, 7.03; N, 9.35. MP 51-54°C.

Example 70

Preparation of dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-hexyl)-amine



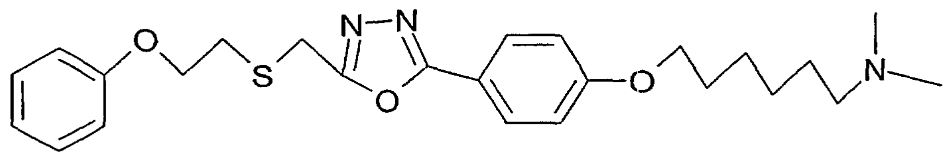
a) 2-[4-(6-Chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.243 g, 0.739 mmol) and 1-bromo-6-chloro-hexane (0.221 g, 1.11 mmol) to give 0.266 g (81%) of 2-[4-(6-chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

[1]H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.6 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 1.7 (m, 4H), 1.4 (m, 4H). IR (KBr, cm^{-1}) 3456, 2936, 2866, 1615, 1586, 1503, 1466, 1258, 1239, 1176, 1007, 843, 764. MS (ESI) m/e 447. Anal. Calcd for $C_{23}H_{27}N_2ClO_3S$: C, 61.80; H, 6.09; N, 6.27. Found C, 61.62; H, 5.55; N, 6.21.

b) Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-hexyl)-amine

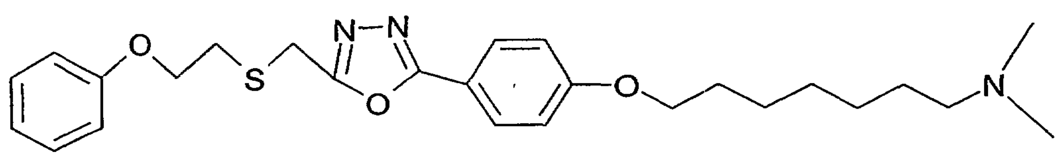


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(6-chloro-hexyloxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.266g, 0.595 mmol) to give 0.116 g (43%) of the title compound.

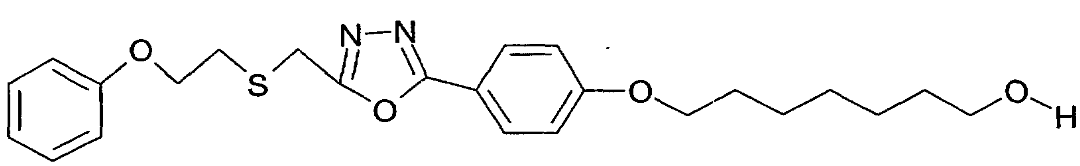
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.4 (m, 4H), 1.3 (m, 2H). IR (KBr, cm^{-1}) 1611, 1602, 1587, 1500, 1466, 1249, 1175, 1024, 756. MS (ESI) m/e 456. Anal. Calcd for $C_{25}H_{33}N_3O_3S$: C, 65.90; H, 7.30; N, 9.22. Found C, 65.37; H, 7.16; N, 9.08.

Example 71

Preparation of dimethyl-(7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptyl)-amine



a) 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol

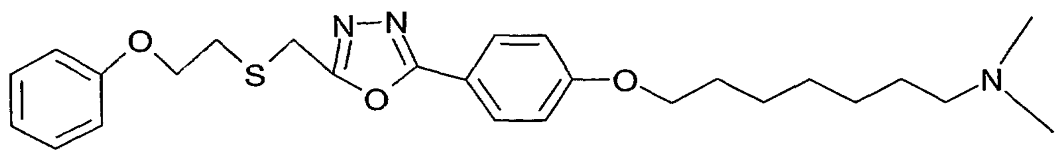


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.260 g, 0.792 mmol) and 7-bromo-heptan-1-ol (0.232 g,

1.19 mmol) to give 0.164 g (47%) of 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, 9 Hz), 6.9 (m, 3H), 4.3 (s, 1H) 4.2 (m, 4H), 4.0 t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz), 1.7 (m, 2H), 1.2-1.4 (m, 8H). IR (KBr, cm^{-1}) 3622, 3011, 2936, 2861, 1613, 1602, 1499, 1469, 1256, 1224, 1174, 1034. MS (ESI) m/e 443. Anal. Calcd for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83; N, 6.33. Found C, 63.3; H, 6.72; N, 5.91.

b) Dimethyl-(7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptyl)-amine

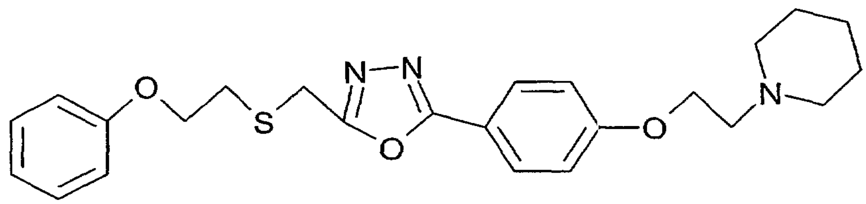


Methanesulfonyl chloride (0.046 g, 0.407 mmol) was added dropwise to a solution of 7-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-heptan-1-ol (0.164 g, 0.374 mmol) and triethylamine (0.045 g, 0.444 mmol) in dichloromethane (20 mL). The mixture was stirred at room temperature for 5 min and concentrated to dryness to give the crude mesylate. The crude solid was dissolved in methanol (10 mL) in a sealed tube and dimethylamine was added (5 mL). The mixture was heated to 80° overnight and concentrated to dryness. The crude solid was dissolved in ethyl acetate and washed with water, brine, dried over sodium sulfate, filtered and concentrated to dryness. The solid was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate followed by 90% $CHCl_3$ and 10% 2M NH_3 in methanol to give 0.063 g (36%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (t, 2H, J=7 Hz), 2.1 (s, 6H), 1.7 (m, 2H), 1.2-1.4 (m, 8H). IR (KBr, cm^{-1}) 2925, 2854, 2762, 1611, 1500, 1254, 1175, 750. MS (ESI) m/e 470. Anal. Calcd for $C_{26}H_{35}N_3O_3S$: C, 66.49; H, 7.51; N, 8.95. Found C, 64.78; H, 7.57; N, 8.44. HPLC 90%. MP=39-40°C.

Example 72

Preparation of 1-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine

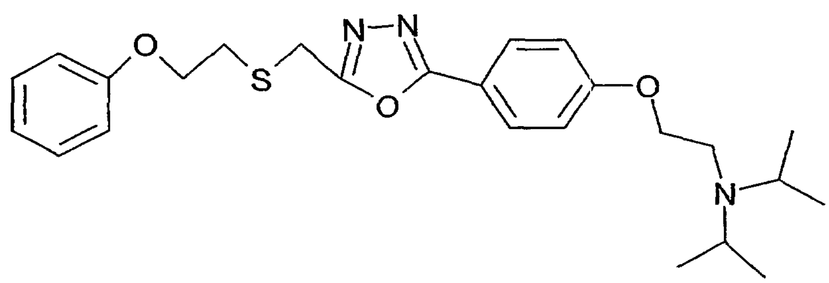


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.202 g, 0.615 mmol) and 1-(2-chloroethyl)piperidine monohydrochloride (0.17 g, 0.922 mmol) to give 0.059 g (22%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.8 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H) 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 2H), 2.4 (m, 4H), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm^{-1}) 2940, 1613, 1499, 1255, 1245, 1175. MS (ESI) m/e 440. Anal. Calcd for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found C, 64.56; H, 6.61; N, 9.42. HPLC 100%. MP = 70°C.

Example 73

Preparation of diisopropyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine



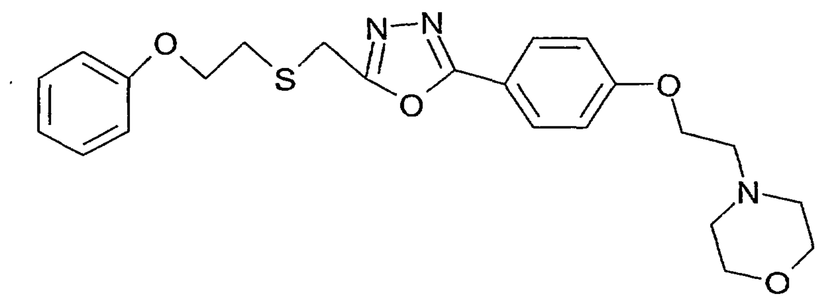
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.223 g, 0.679 mmol) and (2-chloro-ethyl)-diisopropyl-amine, monohydrochloride (0.204 g, 1.02 mmol) to give 0.178 g (58%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H J=7 Hz), 3.0 (m, 4H), 2.8 (t, 2H, J=7 Hz), 1.0 (d,

12H, J=6 Hz). IR (KBr, cm^{-1}) 3632, 3432, 3013, 2945, 2838, 1602, 1464, 13333, 1242. MS (ESI) m/e 456. Anal. Calcd for $C_{25}H_{33}N_3O_3S$: C, 65.90; H, 7.30; N, 9.22. Found C, 65.68; H, 7.16; N, 9.17. MP=42-45°C.

Example 74

Preparation of 4-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-morpholine

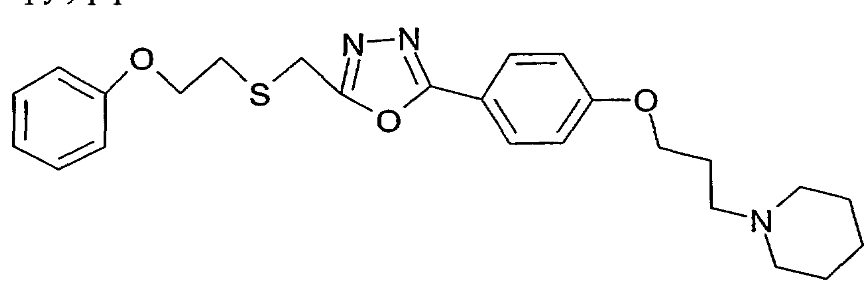


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.266 g, 0.81mM) and 4-(2-chloro-ethyl)-morpholine monohydrochloride (0.226.g, 1.22 mmol) to give 0.225 g (63%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.6 (t, 4H, J=4 Hz), 3.0 (t, 2H, J=6 Hz), 2.7 (t, 2H, J=6 Hz), 2.5 (m, 4H). IR (KBr, cm^{-1}) 1613, 1601, 1588, 1499, 1302, 1253, 1175, 1117. MS (ESI) m/e 442, 440.5. Anal. Calcd for $C_{23}H_{27}N_3O_4S$: C, 62.56; H, 6.16; N, 9.51. Found C, 62.20; H, 6.02; N, 9.39. MP=70-72°C.

Example 75

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine

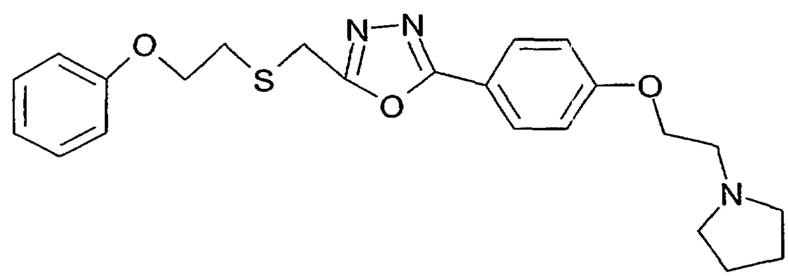


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.218 g, 0.664 mmol) and 1-(3-chloro-propyl)-piperidine, monohydrochloride (0.197 g, 0.996 mmol) to give 0.055 g (18%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 2.4-2.3 (m, 6H), 1.9 (t, 2H, J=7 Hz), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm^{-1}) 3008, 2939, 1614, 1601, 1499, 1303, 1256, 1245, 1175, 839. MS (ESI) m/e 454. Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 65.58; H, 6.65; N, 9.55. Found C, 65.34; H, 6.65; N, 8.95. MP=65°C.

Example 76

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole

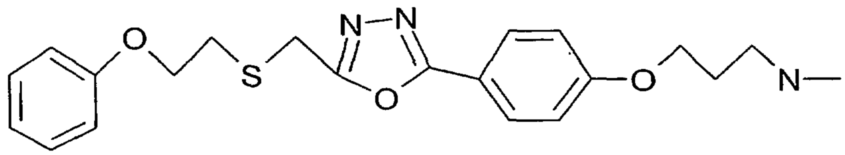


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 66c, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.216 g, 0.658 mmol) and 1-(2-chloro-ethyl)-pyrrolidine, monohydrochloride (0.168 g, 0.987 mmol) to give 0.052 g (18%) of the title compound.

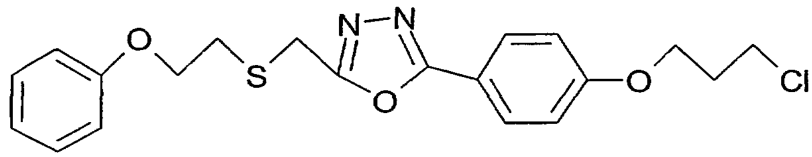
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.8 (m, 2H), 2.5 (m, 4H), 1.6(m, 4H). IR (KBr, cm^{-1}) 1614, 1500, 1246, 1175. MS (ESI) m/e 426. Anal. Calcd for $C_{23}H_{27}N_3O_3S$: C, 64.92; H, 6.40; N, 9.87. Found C, 64.92; H, 6.44; N, 9.76. MP=65°C.

Example 77

Preparation of methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



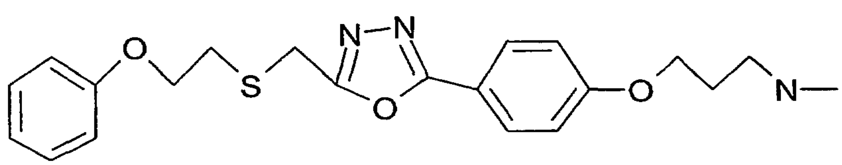
a) 2-[4-(3-Chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (2.396 g, 7.30 mmol) and 1-bromo-3-chloro-propane (1.72 g, 10.9 mmol) to give 1.60 g (54%) of 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.8 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (m, 2H). MS (ESI) m/e 405.

b) Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

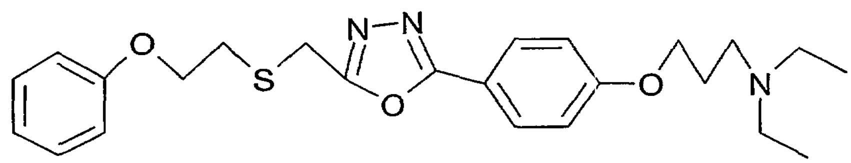


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.247 g, 0.61 mmol) and methylamine (40% weight in water, 2 mL, 26 mmol). HPLC chromatography on the material previously purified by silica chromatography and combination of various lots gave 190 mg of material as the TFA salt which was desalted to the free amine by washing with 1N NaOH, dried over sodium sulfate, filtered and concentrated to dryness to give 0.088 g (14%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=7 Hz), 2.3 (s, 3H), 1.8 (m, 2H). IR (KBr, cm^{-1}) 1677, 1611, 1500, 1254, 1205, 1176, 1131, 835, 754, 722. MS (ESI) m/e 400, 398. Anal. Calcd for $C_{21}H_{25}N_3O_3S$: C, 63.14; H, 6.31; N, 10.52. Found C, 61.78; H, 5.92; N, 9.91. MP=40-44°C. HPLC 100%.

Example 78

Preparation of diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

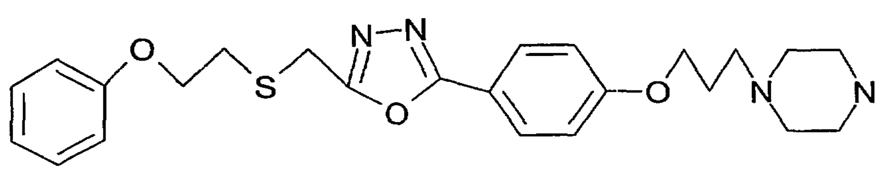


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.230 g, 0.568 mmol) and diethylamine (1.04 g, 14.2 mmol) to give 0.127 g (50%) of the title compound.

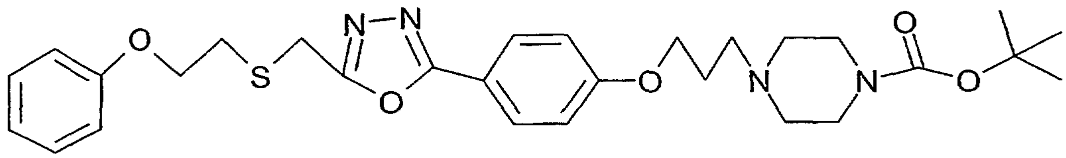
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.5 (m, 4H), 1.8 (t, 2H, J=6 Hz), 0.9 (t, 6H, J=7 Hz). IR (KBr, cm^{-1}) 2973, 1613, 1602, 1499, 1256, 1245, 1174. MS (ESI) m/e 442. Anal. Calcd for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52. Found C, 65.19; H, 7.17; N, 9.41. MP=27-31°C.

Example 79

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine



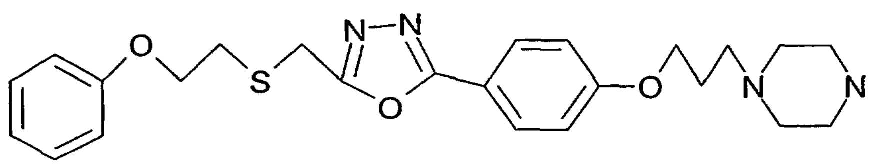
a) 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.241 g, 0.595.mmol) and piperazine-1-carboxylic acid tert-butyl ester (0.111 g, 0.595 mmol) to give 0.096 g (29%) of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=5 Hz), 3.3 (m, 4H), 3.0 (t, 2H, J=6 Hz), 2.4 (m, 2H), 2.3 (m, 4H), 1.9 (m, 2H), 1.4 (s, 9H). MS (ESI) m/e 555. Anal. Calcd for $C_{29}H_{38}N_4O_5S$: C, 62.79; H, 6.90; N, 10.10. Found C, 61.53; H, 6.70; N, 9.73. HPLC 100%.

b) 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine

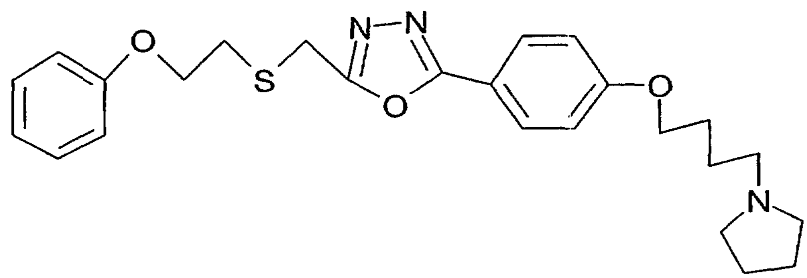


A solution of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester (20a) (0.115 g, 0.20 mmol) and trifluoroacetic acid (5 mL) in 5 mL CH_2Cl_2 was stirred at 5°C for 1 hr. The reaction mixture was concentrated to dryness and extracted into ethyl acetate. The organic extract was washed with $NaHCO_3$, brine, dried over sodium sulfate, filtered and concentrated to give 0.065 g which was purified directly by column chromatography on silica gel (elution with ethyl acetate and toluene followed by 90 chloroform/10 ammonia (2M methanol) to give 0.044 g (47%) of the title product.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz)), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 4H), 2.4 (t, 2H, J=7 Hz), 2.3 (m, 4H), 1.8 (m, 2H). MS (ESI) m/e 455. HPLC 100%.

Example 80

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole

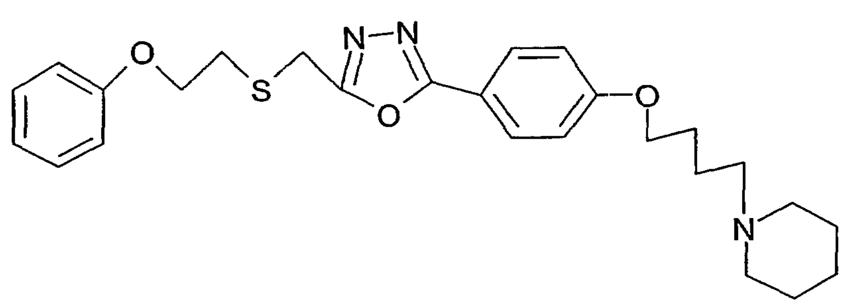


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.235 g, 0.561 mmol) and pyrrolidine (0.099 g, 1.4 mmol) to give 0.145 g (57%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz)), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.4 (m, 6H), 1.8 (m, 2H), 1.7 (m, 4H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 2932, 2563, 2467, 1617, 1500, 1257, 1248. MS (ESI) m/e 454. Anal. Calcd for $C_{25}H_{31}N_3O_3S$: C, 66.20; H, 6.89; N, 9.26. Found C, 65.98; H, 6.90; N, 9.13. M.P.=45°.

Example 81

Preparation of 1-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine

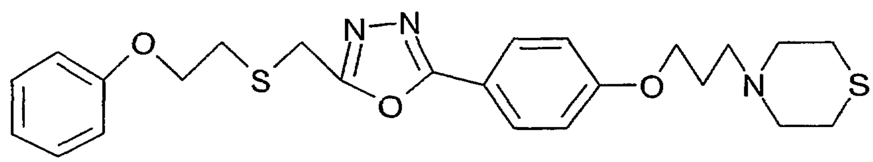


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.232 g, 0.554 mmol) and piperidine (0.118 g, 1.38 mmol) to give 0.041 g (16%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz)), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.3 (m, 6H), 1.7 (m, 2H), 1.6 (m, 2H), 1.5 (m, 4H), 1.4 (m, 2H). IR (KBr, cm^{-1}) 2923, 1610, 1601, 1586, 1500, 1467, 1304, 1256, 1248, 1174, 1031. MS (ESI) m/e 470. Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found C, 66.16; H, 6.91; N, 8.80. M.P.=57-62°C.

Example 82

Preparation of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-thiomorpholine

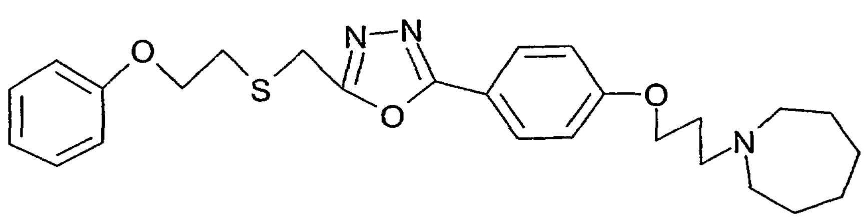


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.248 g, 0.612 mmol) and thiomorpholine (0.157 g, 1.53mM) to give 0.136 g (47%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz)), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 8H), 2.4 (t, 2H, J=7 Hz), 1.9 (m, 2H). IR (KBr, cm^{-1}) 2922, 2810, 2775, 1611, 1601, 1590, 1502, 1491, 1468, 1256, 1244, 1176, 837, 766. MS (ESI) m/e 472, 470. Anal. Calcd for $C_{24}H_{29}N_3O_3S_2$: C, 61.12; H, 6.20; N, 8.91. Found C, 60.85; H, 6.26; N, 8.75. M.P.=85°C.

Example 83

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane

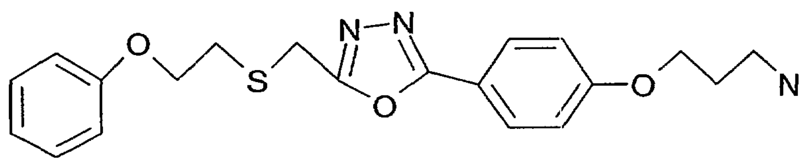


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.213 g, 0.526 mmol) and azepane (1.30 g, 13.1 mmol) to give 0.103 g (42%) of the title compound.

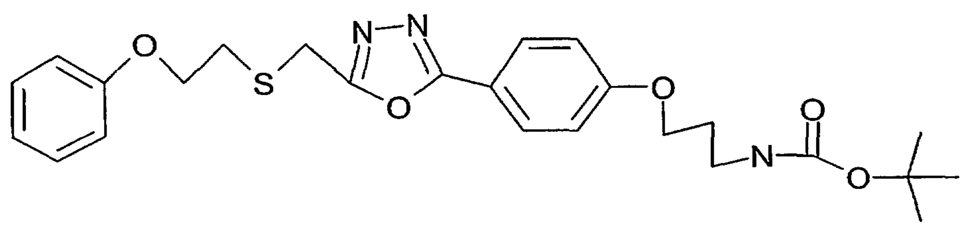
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 6H), 1.8 (m, 2H), 1.5 (m, 8H). IR (KBr, cm^{-1}) 2927, 2905, 1614, 1497, 1468, 1251, 1181, 1171, 1036, 1029, 747, 689. MS (ESI) m/e 468. Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.98. Found C, 66.48; H, 6.94; N, 8.91. M.P.=50°C.

Example 84

Preparation of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine



a) (3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert-butyl ester

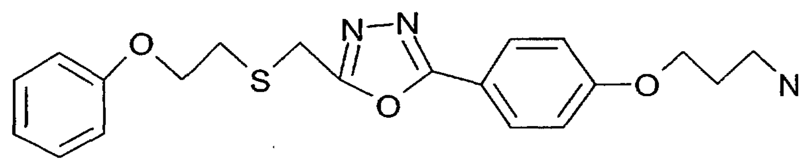


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.501 g, 1.52 mmol) and (3-bromo-propyl)-carbamic acid tert-butyl ester (0.545 g, 2.28 mmol) to give the BOC protected product which was purified by column chromatography on silica gel (elution with ethyl acetate/toluene) to give 0.617 g (84%) of the (3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert-butyl ester.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.0 (t, 2H, J=6 Hz), 3.1 (q, 2H, J=6 Hz), 3.0 (t, 2H, J=6

Hz), 1.8 (m, 2H), 1.4 (s, 9H). IR (KBr, cm^{-1}) 3400, 1692, 1609, 1524, 1501, 1248, 1242, 1176, 844, 764. MS (ESI) m/e 486. Anal. Calcd for $C_{25}H_{31}N_3O_5S$: C, 70.12; H, 5.23; N, 9.08. Found C, 69.86; H, 5.19; N, 8.92.

b) 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine

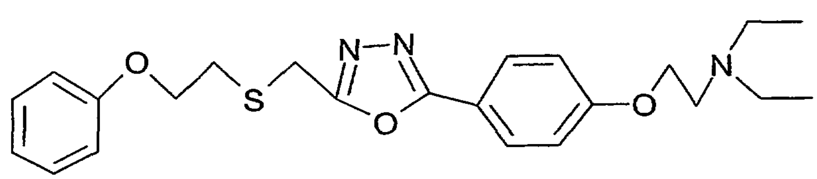


A solution of (3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-carbamic acid tert -butyl ester (0.600 mg, 1.23 mmol) in TFA (7 mL) and CH_2Cl_2, (5 mL) was stirred at 5°C for 1 hr. The reaction mixture was concentrated to dryness and extracted into ethyl acetate. The organic extract was washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give 0.300 g. Elemental analysis indicated the presence of fluorine. The material was dissolved in water, ethyl acetate and a minimum amount of methanol to solubilize the material. The mixture was washed with 1N NaOH, dried over sodium sulfate, and concentrated to give 0.183 g, (38%) of the 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.7 (t, 2H, J=7 Hz), 1.8 (m, 2H). IR (KBr, cm^{-1}) 3004, 2972, 2928, 2902, 1616, 1504, 1474, 1252, 1175, 833. MS (ESI) m/e 386. Anal. Calcd for $C_{20}H_{23}N_3O_3S$: C, 62.31; H, 6.01; N, 10.90. Found C, 61.08; H, 5.99; N, 10.49. HPLC 100%. M.P.=30-35°.

Example 85

Preparation of diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine

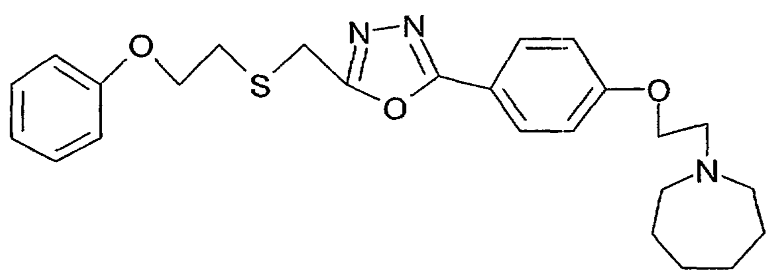


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.206 g, 0.627 mmol) and (2-bromo-ethyl)-diethyl-amine hydrobromide to give 0.041 g (15%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.8 (m, 2H), 2.6 (m, 4H), 1.0 (t, 6H, J=7 Hz). IR (KBr, cm^{-1}) 1614, 1498, 1258, 1176, 1172, 752. MS (ESI) m/e 429. Anal. Calcd for $C_{23}H_{29}N_3O_3S$: C, 64.61; H, 6.84; N, 9.83. Found C, 64.37; H, 6.85; N, 9.77. M.P.=32-35°C.

Example 86

Preparation of 1-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane

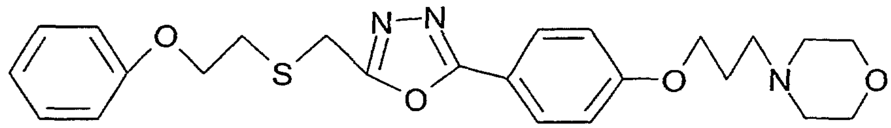


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.197 g, 0.599 mmol) and 1-(2-chloro-ethyl)-azepane hydrochloride (0.178 g, 0.899 mmol) to give crude material that was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH_3 in methanol to give 0.216 g (79%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.9 (m, 2H), 2.7 (m, 4H), 1.5 (m, 8H). IR (KBr, cm^{-1}) 2917, 1613, 1604, 1500, 1261, 1247, 1176, 749. MS (ESI) m/e 454. Anal. Calcd for $C_{25}H_{31}N_3O_3S$: C, 66.20; H, 6.89; N, 9.26. Found C, 66.17; H, 6.96; N, 9.16. M.P.=40°C.

Example 87

Preparation of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-morpholine

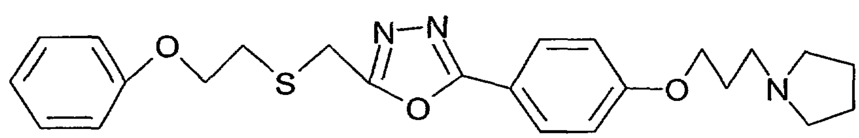


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.222 g , 0.548 mmol) and morpholine (0.119 g, 1.37 mmol) to give 0.078 g (31%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.6 (t, 4H, J=4 Hz) 3.0 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=7 Hz), 2.3 (m, 4H), 1.9 (m, 2H). IR (KBr, cm^{-1}) 3436, 2965, 2943, 2926, 2863, 2810, 1609, 1500, 1468, 1297, 1256, 1242, 1174, 1115, 838, 764. MS (ESI) m/e 456, 454. Anal. Calcd for $C_{24}H_{29}N_3O_4S$: C, 63.27; H, 6.41; N, 9.22. Found C, 63.06; H, 6.60; N, 9.04. M.P.=65°C.

Example 88

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[1,3,4]oxadiazole

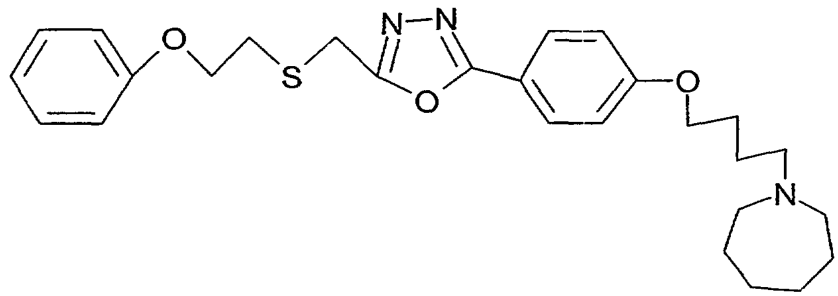


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.222 g, 0.548 mmol) and pyrrolidine (0.097 g, 1.37 mmol) to give 0.131 g (54%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=7 Hz), 2.5 (m, 4H), 1.9 (m, 2H), 1.7 (m, 4H). IR (KBr, cm^{-1}) 2972, 2944, 2928, 2865, 2792, 1613, 1584, 1500, 1478, 1466, 1402, 1253, 1183, 1152, 1006, 849, 757. MS (ESI) m/e 440, 439. Anal. Calcd for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found C, 65.28; H, 6.70; N, 9.45. M.P.=70°C.

Example 89

Preparation of 1-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane

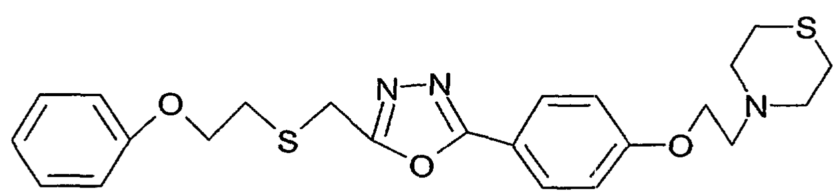


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.227 g, 0.542 mmol) and azepane (0.56 g, 5.64 mmol) to give 0.091 g (35%) of the title compound.

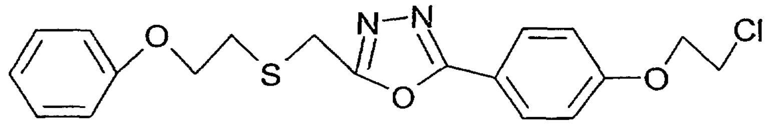
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.5 (m, 6H), 1.7 (m, 2H), 1.5 (m, 10H). IR (KBr, cm^{-1}) 2930, 1610, 1493, 1248, 1175, 837. MS (ESI) m/e 482, 480. Anal. Calcd for $C_{27}H_{35}N_3O_3S$: C, 67.33; H, 7.32; N, 8.72. Found C, 67.35; H, 7.25; N, 8.91. M.P.=35-38°C.

Example 90

Preparation of 4-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-thiomorpholine



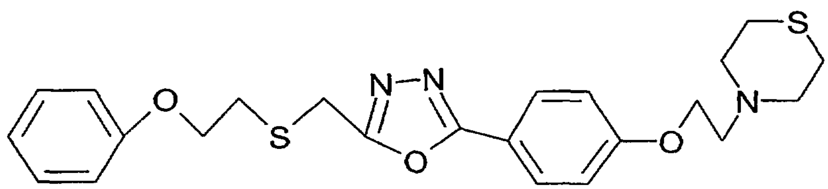
a) 2-[4-(2-Chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (1.491 g, (4.54.mmol) and 1-bromo-2-chloro-ethane (0.98 g, 6.81 mmol) to give 1.216 g (68%) of 2-[4-(2-chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.3 (t, 2H, J=5 Hz), 4.2 (m, 4H), 4.0 (t, 2H, J=5 Hz), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 3439, 2965, 2929, 2916, 1619, 1603, 1586, 1499, 1465, 1249, 1177, 1088, 1023, 1008, 756. MS (ESI) m/e 391. Anal. Calcd for $C_{19}H_{19}ClN_2O_3S$: C, 58.38; H, 4.90; N, 7.17. Found C, 58.27; H, 5.01; N, 7.07.

b) 4-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-thiomorpholine

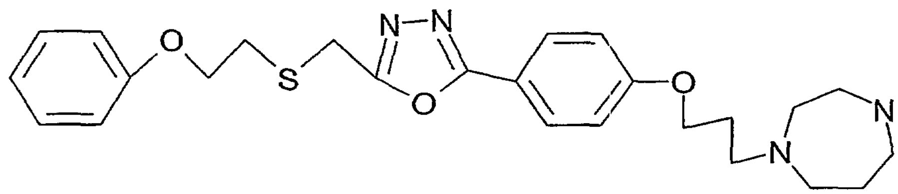


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(2-chloro-ethoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.215 g, 0.55 mmol) and thiomorpholine (0.141 g, 1.37 mmol) to give 0.066 g (26%) of the title product.

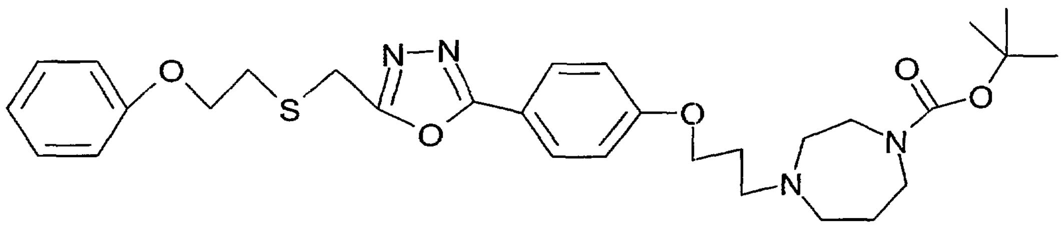
^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz) 2.8 (m, 6H), 2.6 (m, 4H). IR (KBr, cm^{-1}) 2926, 2807, 1614, 1503, 1459, 1297, 1253, 1173, 834, 754. MS (ESI) m/e 458, 456. Anal. Calcd for $C_{23}H_{27}N_3O_3S_2$: C, 60.37; H, 5.95; N, 9.18. Found C, 59.64; H, 5.61; N, 8.94. M.P.=60°C. HPLC 100%.

Example 91

Preparation of 1-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane



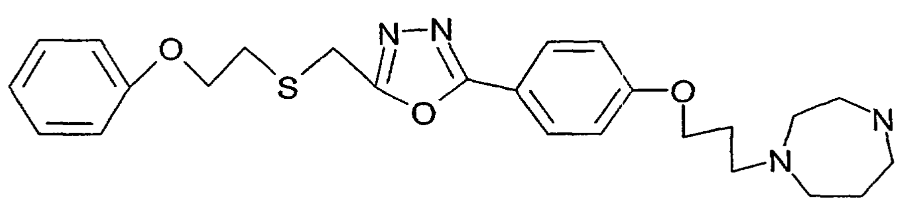
a) 4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68a, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.223 g, 0.679 mmol) and 4-(3-chloro-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester (0.376 g, 1.36 mmol) to give crude material that was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH_3 in methanol) to give 0.49 g (100%) of 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=7 Hz), 3.6 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz) 2.6 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H), 1.4 (s, 9H). MS (ESI) m/e 569.

b) 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane

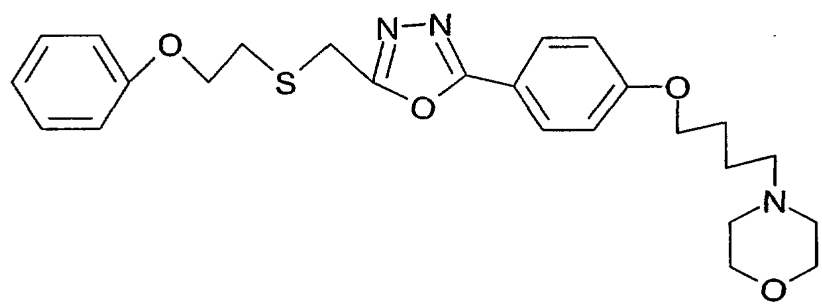


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 79b, from 4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester (0.49 g, 0.862 mmol) and trifluoroacetic acid (5 mL) to give 0.136 g (34%) of the title product.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz) 2.8 (m, 3H), 2.6 (m, 6H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 2337, 1671, 1613, 1499, 1256, 1245, 1175. MS (ESI) m/e 469. Anal. Calcd for $C_{25}H_{32}N_4O_3S$: C, 64.08; H, 6.88; N, 11.95. Found C, 58.41; H, 6.35; N, 10.64. HPLC 100%.

Example 92

Preparation of 4-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-morpholine

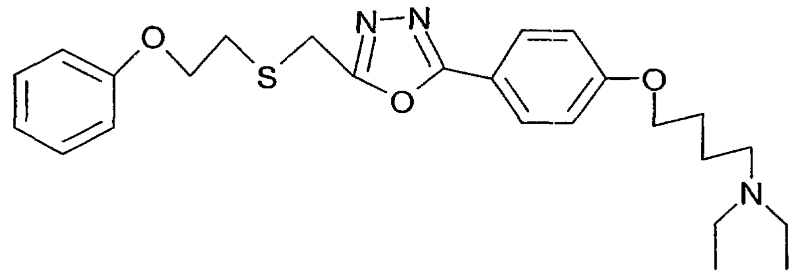


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.225 g, 0.537 mmol) and morpholine (0.117 g, 1.34 mmol) to give 0.144 g (57%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.5 (m, 4H), 3.0 (t, 2H, J=6 Hz) 2.3 (m, 6H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 2935, 2852, 2811, 1611, 1499, 1303, 1249, 1174, 1118, 836. MS (ESI) m/e 470, 468. Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95. Found C, 63.83; H, 6.72; N, 8.93. M.P.=64-67°C.

Example 93

Preparation of diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine

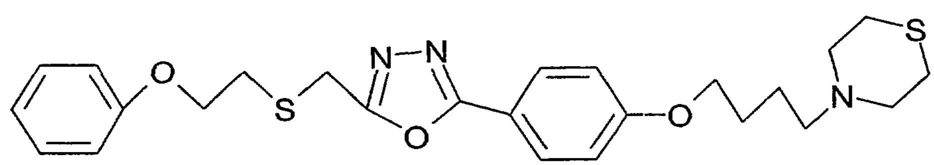


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.225 g, 0.537 mmol) and diethyl amine (0.989 g, 13.4 mmol) to give 0.090 g (37%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz) 2.4 (m, 6H), 1.7 (m, 2H), 1.6 (m, 2H), 1.0 (t, 6H, J=7 Hz). IR (KBr, cm^{-1}) 2929, 2799, 1610, 1500, 1248, 1174, 1005, 837. MS (ESI) m/e 456. Anal. Calcd for $C_{25}H_{33}N_3O_3S$: C, 65.90; H, 7.30; N, 9.22. Found C, 63.98; H, 7.08; N, 9.72. M.P.=35-38°C. HPLC 99%.

Example 94

Preparation of 4-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-thiomorpholine



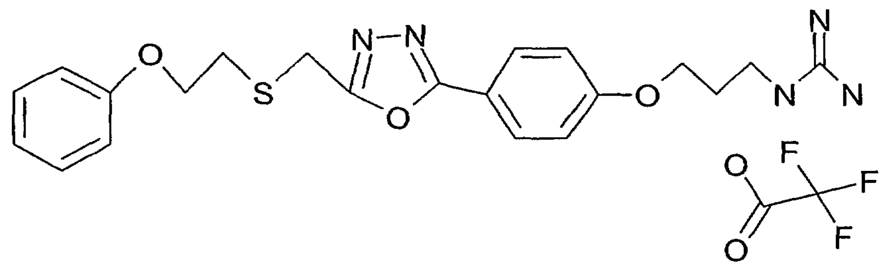
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 68b, from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.313 g, 0.747 mmol) and thiomorpholine (0.154 g, 1.49 mmol) to give 0.219 g (60%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 8H), 2.3 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H). IR (KBr, cm^{-1}) 3000, 2873, 2816, 1613, 1588, 1499,

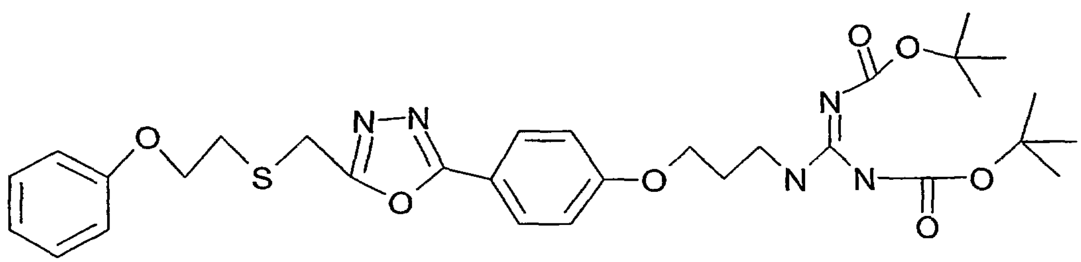
1256, 1245, 1174, 1006, 839. MS (ESI) m/e 486, 484. Anal. Calcd for $C_{25}H_{31}N_3O_3S_2$: C, 61.83; H, 6.43; N, 8.65. Found C, 61.66; H, 6.44; N, 8.59. M.P.=58°C.

Example 95

Preparation of N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, trifluoroacetic acid salt



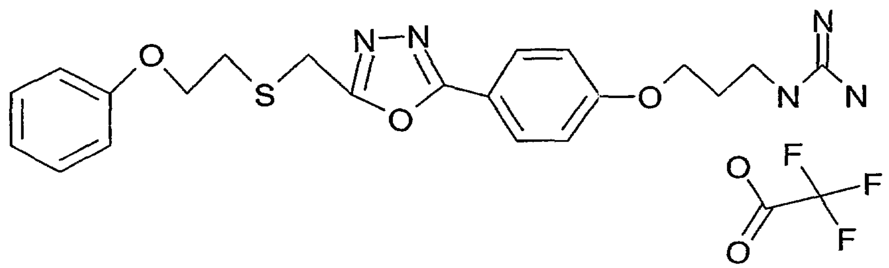
a) N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester



A solution of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propylamine (Example 85b) (0.142 g, 0.368 mmol) and 1,3-bis(*t*-butoxycarbonyl)-2-methyl-2-thiopseudourea (0.112 g, 0.387 mmol) in acetonitrile (7 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$. The aqueous layer was extracted once with ethyl acetate. The combined organics were washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/toluene) to give 0.119 g (52%) of N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester (40a).

^{1}H NMR (DMSO-d6) δ 8.5 (m, 1H), 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.5 (m, 2H), 3.0 (t, 2H, J=6 Hz) 2.0 (m, 2H), 1.5 (s, 9H), 1.4 (s, 9H). MS (ESI) m/e 628.

b) N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, trifluoroacetic acid salt

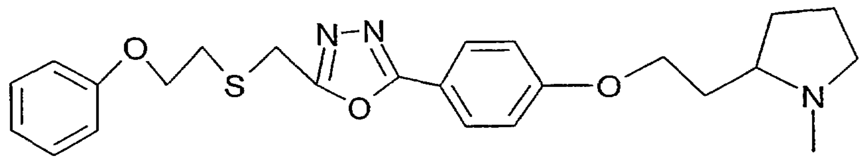


N-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-methanetriamine, di-carboxylic acid tert-butyl ester (0.253 g, 0.403 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 5°C. Trifluoroacetic acid (5 mL) was added and the mixture was stirred at 5°C for 1 hr and at room temperature for 1 hr. The mixture was concentrated to dryness, diluted with ethyl acetate and washed with 1N NaOH. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate, filtered, and concentrated to 0.073 g. Due to low recovery, the aqueous layer was extracted 4 times with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to 0.186 g. The combined residues were purified by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH_3 in methanol) to give 0.106 g that was recrystallized from 1 mL ethyl acetate and 5 mL ethyl ether to give 0.075 g (34%) of the title compound.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.6 (m, 1H), 7.2 (m, 3H), 7.1 (m, 3H), 7.0 (s, 1H), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz), 2.0 (m, 2H). IR (KBr, cm^{-1}) 3400, 3110, 1674, 1636, 1612, 1500, 1252, 1205, 1176, 1136. MS (ESI) m/e 428. Anal. Calcd for $C_{23}H_{26}N_5F_3O_5S$: C, 51.01; H, 4.84; N, 12.93; F, 10.52. Found C, 45.58; H, 4.91; N, 13.21; F, 11.96. M.P.=100°C. HPLC 100%.

Example 96

Preparation of 2-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole

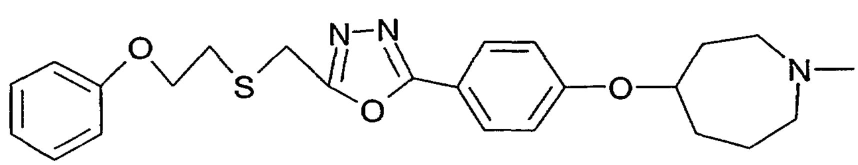


A mixture of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.346 g, 1.05 mmol) and 60% NaH (0.121 g, 3.15 mmol) was stirred at 5°C for 2 minutes in DMF (5 mL). Added 2-(2-chloro-ethyl)-1-methyl-pyrrolidine (0.291 g, 1.58 mmol) and heated the mixture to 100°C for 10 hrs. Diluted with ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed 3 X water, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH_3 in methanol) to give 0.054 g, (12%) of the title compound and material that was a mixture of 2 products, one being the title compound and a second product of the reaction (Example 97), see procedure for Example 97.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (m, 2H), 3.0 (m, 3H), 2.3 (s, 3H), 2.2 (m, 1H), 2.1 (m, 2H), 2.0 (m, 1H), 1.7 (m, 3H), 1.5 (m, 1H). IR (KBr, cm^{-1}) 3410, 3000, 2910, 2800, 1610, 1500, 1468, 1257, 1241, 1173, 764. MS (ESI) m/e 440. Anal. Calcd for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found C, 63.09; H, 6.22; N, 8.96. M.P.=46-50°C. HPLC 94%.

Example 97

Preparation of 1-methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-azepane



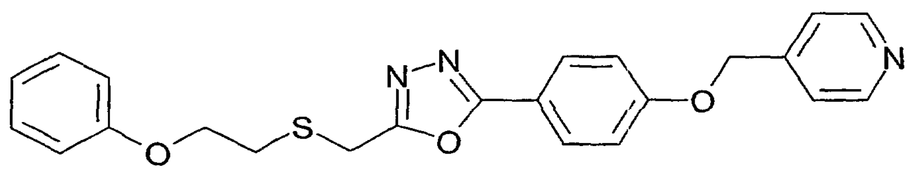
Prepared in the same manner as exemplified in Example 96 and isolated as a by-product of the reaction mixture. The mixture isolated via chromatography from procedure 96 was purified a second time using a Waters Preparatory 2000 with a Kromasil silica column (5 X 25 cm) (elution with 50/50 ethyl acetate/dichloromethane/1%

dimethylethylamine to give 0.209 g (12%) of the title compound and 0.200 g (12%) of the compound of Example 96.

^{1}H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.7 (m, 1H), 4.2 (m, 4H), 3.0 (m, 2H), 2.65 (m, 1H), 2.6 (m, 2H), 2.5 (m, 1H), 2.3 (s, 3H), 2.1 (m, 2H), 1.9 (m, 1H), 1.8 (2H), 1.6 (m, 1H). IR (KBr, cm^{-1}) 2923, 1612, 1602, 1587, 1499, 1465, 1295, 1237, 1174, 1002. MS (ESI) m/e 440. Anal. Calcd for $C_{24}H_{29}N_3O_3S$: C, 65.58; H, 6.65; N, 9.56. Found C, 66.35; H, 6.83; N, 9.05. M.P.=60-61°C. *HPLC 100%.*

Example 98

Preparation of 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxymethyl}-pyridine

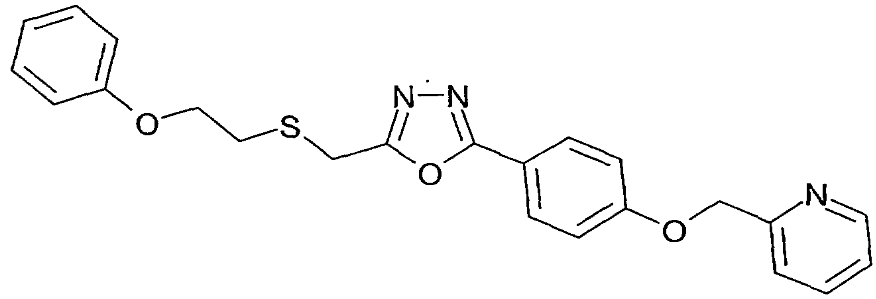


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.303 g, 0.923 mmol) and 4-bromomethyl-pyridine hydrobromide salt (0.350 g, 1.38 mmol) to give a crude solid which was purified directly by column chromatography on silica gel (elution with ethyl acetate/toluene followed by 90% chloroform/10% 2M NH_3 in methanol to give material which was recrystallized from ethyl acetate, methanol, and ethyl ether to give 0.233 g (59%) of the title compound.

^{1}H NMR (DMSO-d6) δ 8.6 (d, 2H, J=5 Hz), 7.9 (d, 2H, J=9 Hz), 7.4 (d, 2H, J=5 Hz), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 1603, 1501, 1264, 1249, 1172, 1005, 755. MS (ESI) m/e 420. Anal. Calcd for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.04; N, 10.02. Found C, 65.82; H, 5.11; N, 10.34. M.P.=80-90°C.

Example 99

Preparation of 2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxymethyl}-pyridine

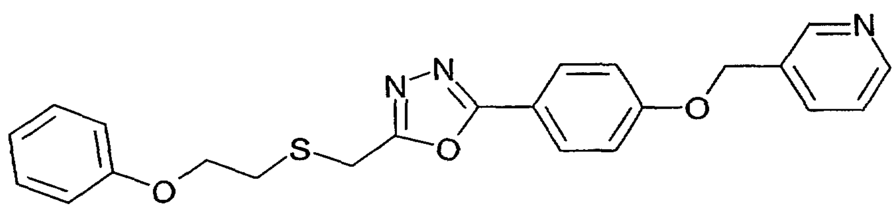


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.269 g, 0.819 mmol) and 2-bromomethyl-pyridine hydrobromide salt (0.311 g, 1.23 mmol) to give 0.146 g (42%) of the title compound.

^{1}H NMR (DMSO-d6) δ 8.6 (m, 1H), 7.9 (m, 3H), 7.5 (d, 1H, J=8 Hz), 7.4 (m, 1H), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 1617, 1589, 1498, 1269, 1249, 1172, 1039, 753. MS (ESI) m/e 420. Anal. Calcd for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.04; N, 10.02. Found C, 65.55; H, 4.88; N, 9.88. M.P.=115°C.

Example 100

Preparation of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxymethyl}-pyridine



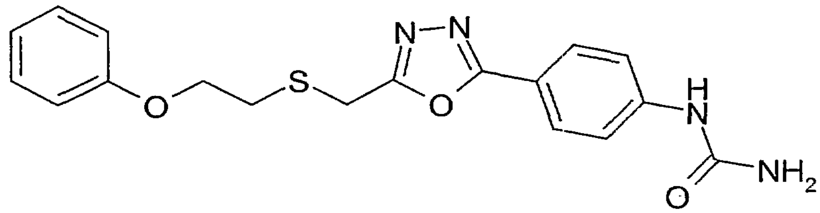
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 96, from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.274 g, 0.834 mmol) and 3-bromomethyl-pyridine hydrobromide salt (0.316 g, 1.25 mmol) to give 0.177 g (50 %) of the title compound.

^{1}H NMR (DMSO-d6) δ 8.7 (d, 1H, J=2 Hz), 8.6 (m, 1H), 7.9 (m, 3H), 7.4 (m, 1H), 7.2 (m, 4H), 6.9 (m, 3H), 5.3 (s, 2H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm^{-1}) 1610, 1588, 1498, 1464, 1421, 1299, 1249, 1173, 1006, 758. MS (ESI) m/e 420. Anal.

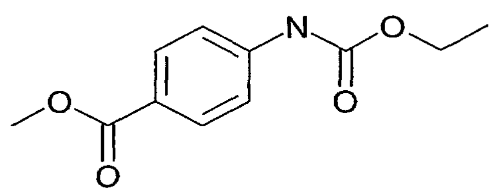
Calcd for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.04; N, 10.02. Found C, 65.83; H, 5.02; N, 10.04. M.P.=111-112°C.

Example 101

Preparation of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea



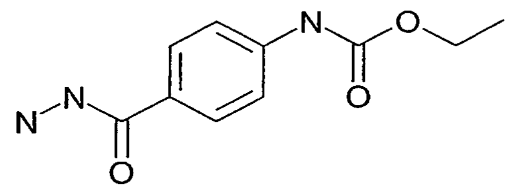
a) 4-Ethoxycarbonylamino-benzoic acid methyl ester



Ethyl chloroformate (16.15 g, 148.85 mmol, 1.5 eq.) was added dropwise via syringe to a solution of methyl 4-aminobenzoate (15.0 g, 99.23 mmol, 1 eq.) in pyridine (400 mL) at 0 °C. After addition was complete, the reaction was allowed to stir and gradually warm to room temperature. After 4 hours, the pyridine was removed *in vacuo* and the residue suspended in water. The aqueous mixture was extracted with 50% Et2O in EtOAc. The combined organic layers were washed with aqueous 1M HCl, saturated sodium bicarbonate, and then brine, dried over MgSO4, filtered, and the solvent removed *in vacuo* to afford 21.79 g (98%) of 4-ethoxycarbonylamino-benzoic acid methyl ester as a yellow solid.

^{1}H NMR (DMSO-d6) δ 10.04 (s, 1H), 7.88 (d, 2H, J=9 Hz), 7.59 (d, 2H, J=9 Hz), 4.15 (q, 2H, J=7 Hz), 3.81 (s, 3H), 1.26 (t, 3H, J=7 Hz). IR (KBr, cm^{-1}) 3318, 1730, 1692, 1596, 1538, 1415, 1298, 1224, 1180, 1057. MS (ES$^+$) m/e 224. MS (ES$^-$) m/e 222. Anal. Calcd for $C_{11}H_{13}NO_4$ C, 59.19; H, 5.87; N, 6.27. Found C, 59.33; H, 5.92; N, 6.30. MP 159-162°C.

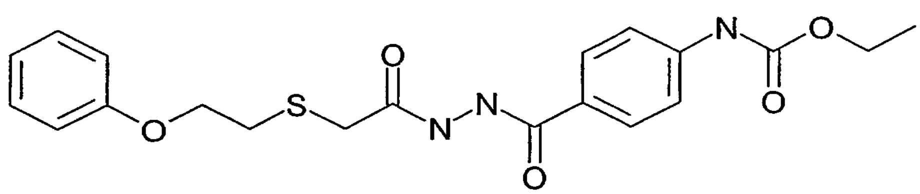
b) (4-Hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester



Hydrazine hydrate (3.59 g, 112.0 mmol, 5 eq.) was added to a solution of 4-ethoxycarbonylamino-benzoic acid methyl ester (5.0 g, 22.40 mmol, 1 eq.) in ethanol. The mixture was heated at 76 °C for 16 h. The solvent was removed in vacuo. The resultant white solid was suspended in EtOAc (150 mL) and heated on a hot plate until ~100 mL remained, then allowed to cool. The resultant precipitate was collected by filtration to give 4.25 g (85%) of (4-hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester as a white solid.

^{1}H NMR (DMSO-d6) δ 9.85 (s, 1H), 9.56 (s, 1H), 7.74 (d, 2H, J=9 Hz), 7.50 (d, 2H, J=9 Hz), 4.52 (br s, 2H), 4.13 (q, 2H, J=7 Hz), 1.25 (t, 3H, J=7 Hz). IR (KBr, cm^{-1}) 3303, 3278, 1715, 1631, 1593, 1525, 1503, 1328, 1228, 1067. MS (ES$^+$) m/e 224. Anal. Calcd for $C_{10}H_{13}N_3O_3$ C, 53.81; H, 5.87; N, 18.82. Found C, 53.52; H, 5.86; N, 19.20. MP softening at 186°C then 193-195°C.

c) (4-{N'-[2-(2-Phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester

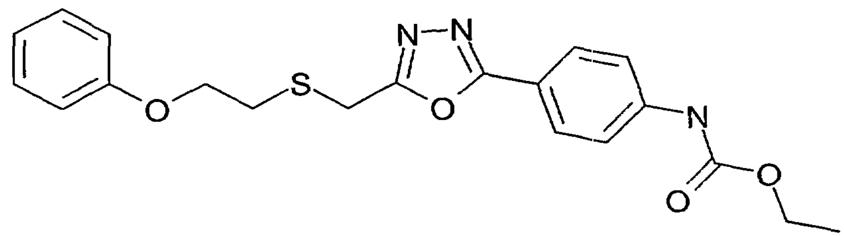


EEDQ (8.30 g, 33.55 mmol, 1.1 eq.) was added as a solid to a solution of (2-Phenoxyethylthio)acetic acid (6.47 g, 30.50 mmol, 1 eq.) in anhydrous 450 mL acetonitrile and 150 mL THF at room temperature. The reaction was stirred at room temperature for 1 h, then (4-hydrazinocarbonyl-phenyl)-carbamic acid ethyl ester (7.49 g, 33.55 mmol, 1.1 eq.) was added as a solid. The mixture was stirred at room temperature for an additional 16 h. The solvent was removed *in vacuo* to afford a tan solid. The solid was suspended in aqueous 1 M HCl and extracted with EtOAc. The organic extract was

washed with water, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, filtered and concentrated to afford an off-white solid. The resulting solid was recrystallized from EtOAc and collected by filtration to afford 10.01 g (79%) of (4-{N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester as an off-white solid.

^{1}H NMR (DMSO-d6) δ 10.28 (s, 1H), 10.05 (s, 1H), 9.94 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.55 (d, 2H, J=9 Hz), 7.29 (m, 2H), 6.95 (m, 3H), 4.16 (m, 4H), 3.32 (s, 2H), 3.04 (t, 2H, J=7 Hz), 1.26 (t, 3H, J=7 Hz). IR ($CHCl_3$, cm^{-1}) 1737, 1525, 1508, 1498, 1215. MS (ES^+) m/e 418. MS (ES^-) m/e 416. Anal. Calcd for $C_{20}H_{23}N_3O_5S$ C, 57.54; H, 5.55; N, 10.06. Found C, 57.18; H, 5.59; N, 10.10.

d) {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester

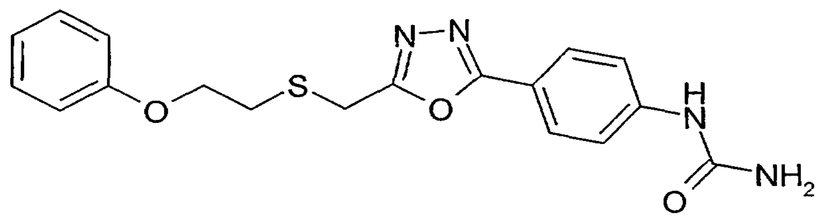


Triphenylphosphine (2.76 g, 10.54 mmol, 1.1 eq.) was added to a suspension of (4-{N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazinocarbonyl}-phenyl)-carbamic acid ethyl ester (4.0 g, 9.58 mmol, 1 eq.) in anhydrous THF (250 mL) at room temerature. Triethylamine (3.49 g, 34.49 mmol, 3.6 eq.) was then added to the mixture via syringe. After stirring for 5 minutes, carbon tetrabromide (3.50 g, 10.54 mmol, 1.1 eq.) was added as a solid with vigorous stirring. The reaction was allowed to stir at room temperature for 16 h. The solvent was removed *in vacuo* leaving a dark brown solid. The solid was purified via silica gel flash chromatography using a step gradient of EtOAc in hexane as the mobile phase to afford 1.93 g (50%) of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester as a yellow solid.

^{1}H NMR (DMSO-d6) δ 10.06 (s, 1H), 7.88 (d, 2H, J=9 Hz), 7.67 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.18 (m, 6H), 3.02 (t, 2H, J=7 Hz), 1.26 (t, 3H, J=7 Hz). IR ($CHCl_3$, cm^{-1}) 3432, 3009, 1737, 1522, 1504, 1242, 1226, 1224, 1216, 1210, 1206, 1182.

MS (ES^+) m/e 400. MS (ES^-) m/e 398. Anal. Calcd for $C_{20}H_{21}N_3O_4S$ C, 60.14; H, 5.30; N, 10.52. Found C, 59.78; H, 5.34; N, 10.41.

e) Preparation of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea

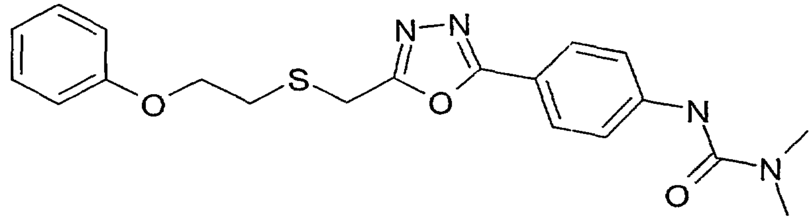


Triethylamine (0.30 g, 3.0 mmol, 1.2 eq.) was added via syringe to a suspension of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.5 mmol, 1 eq.) in anhydrous toluene (10 mL). The mixture was heated to reflux, after 5 minutes, *B*-chlorocatecholborane (0.46 g, 3.0 mmol, 1.2 eq.) was added as a solid and the reaction allowed to stir at refux for 15 minutes.
The reaction was allowed to cool to about 40°C and then ammonia in methanol (1.07 mL of 7M NH3 in MeOH) was added via syringe with vigorous stirring (turning the dark brown solution to a yellow suspension). The suspension was allowed to stir at room temperature for 1.5 h. The resultant suspension was filtered to obtain 1.19 g of a yellow solid, which was purified by recrystallization from ethanol to afford 0.67 g (72%) {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a light yellow solid.

^{1}H NMR (DMSO-d6) δ 8.97 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.61 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.94 (m, 3H), 6.05 (s, 2H), 4.20 (m, 4H), 3.02 (t, 2H, J=7 Hz). IR (KBr, cm^{-1}) 3343, 3175, 1699, 1599, 1530, 1497, 1418, 1242, 843. MS (ES^+) m/e 371. MS (ES^-) m/e 369. Anal. Calcd for $C_{18}H_{18}N_4O_3S$ C, 58.36; H, 4.90; N, 15.12. Found C, 58.21; H, 4.95; N, 14.96. MP >220°C.

Example 102

Preparation of 1,1-dimethyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea

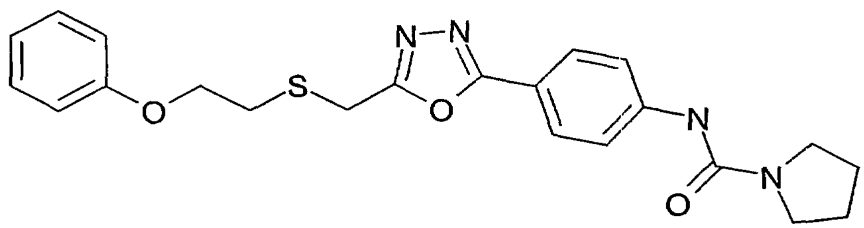


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and dimethylamine (2M in THF, 1.2 mL, 2.4 mmol, 1.2 eq.) to produce 0.53 g (67%) of 1,1-dimethyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an off-white solid.

^{1}H NMR (DMSO-d6) δ 8.68 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.71 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.02 (t, 2H, J=7 Hz), 2.95 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3009, 1674, 1598, 1519, 1498, 1415, 1244, 1173. MS (ES^+) m/e 399. MS (ES^-) m/e 397. Anal. Calcd for $C_{20}H_{22}N_4O_3S$ C, 60.28; H, 5.56; N, 14.06. Found C, 60.26; H, 5.47; N, 13.80. Analytical HPLC 97.3% purity. MP softening at 163°C then 167-169°C.

Example 103

Preparation of pyrrolidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide

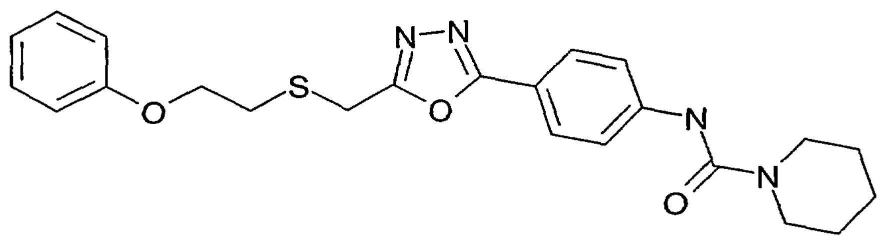


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and pyrrolidine (0.17 g, 2.4 mmol, 1.2 eq.) to produce 0.50 g (59%) of pyrrolidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as an orange/brown solid.

^{1}H NMR (DMSO-d6) δ 8.51 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.76 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.40 (m, 4H), 3.02 (t, 2H, J=7 Hz), 1.86 (m, 4H). IR (KBr, cm^{-1}) 3394, 1660, 1595, 1524, 1497, 1252, 835, 759. MS (ES^+) m/e 425. MS (ES^-) m/e 423. Anal. Calcd for $C_{22}H_{24}N_4O_3S$ C, 62.24; H, 5.70; N, 13.20. Found C, 61.85; H, 5.81; N, 12.93. Analytical HPLC >99% purity. MP 184-185°C.

Example 104

Preparation of piperidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide

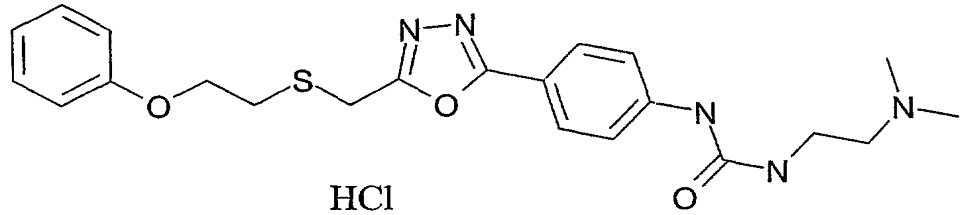


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and piperidine (0.20 g, 2.4 mmol, 1.2 eq.) to produce 0.33 g (38%) of piperidine-1-carboxylic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a light yellow solid.

^{1}H NMR (DMSO-d6) δ 8.84 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.44 (m, 4H), 3.02 (t, 2H, J=7 Hz), 1.54 (m, 6H). IR ($CHCl_3$, cm^{-1}) 3005, 2944, 2860, 1662, 1599, 1515, 1497, 1420, 1312, 1241, 1181. MS (ES^+) m/e 439. MS (ES^-) m/e 437. Anal. Calcd for $C_{23}H_{26}N_4O_3S$ C, 62.99; H, 5.98; N, 12.78. Found C, 62.59; H, 5.87; N, 12.48. Analytical HPLC 99% purity. MP softening at 128°C then 132-134°C.

Example 105

Preparation of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea hydrochloride



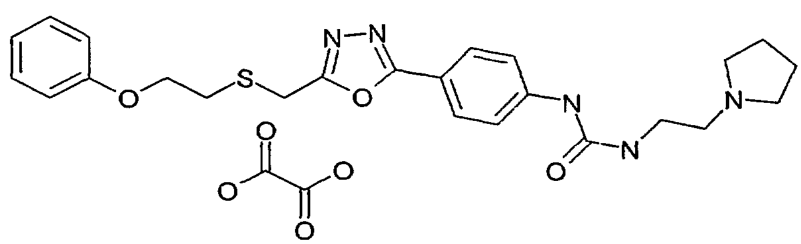
HCl

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (1.00 g, 2.5 mmol, 1 eq.) and *N,N*-dimethylethylenediamine (0.26 g, 3.0 mmol, 1.2 eq.) to afford 0.93 g (85%) of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification via silica gel flash chromatography using 10% 2M NH3 in methanol in chloroform as the mobile phase. The free base was converted to the hydrochloride salt by adding 1.2 eq. of 4M HCl in 1,4-dioxane (0.33 mL) dropwise to an EtOAc solution of the free base (0.48 g). The resulting white solid was quickly collected by filtration and dried to give 0.26 g of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea hydrochloride as a white solid.

^{1}H NMR (DMSO-d6) δ 10.06 (s, 1H), 9.70 (s, 1H), 7.84 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.94 (m, 4H), 4.19 (m, 4H), 3.48 (m, 2H), 3.18 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.82 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3302, 3000, 1695, 1602, 1545, 1499, 1318, 1233, 1181. MS (ES^+) m/e 442. MS (ES^-) m/e 440. Anal. Calcd for $C_{22}H_{28}ClN_5O_3S$ C, 55.28; H, 5.90; N, 14.65. Found C, 53.48; H, 5.62; N, 14.60. Analytical HPLC >99% purity.

Example 106

Preparation of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea oxalate

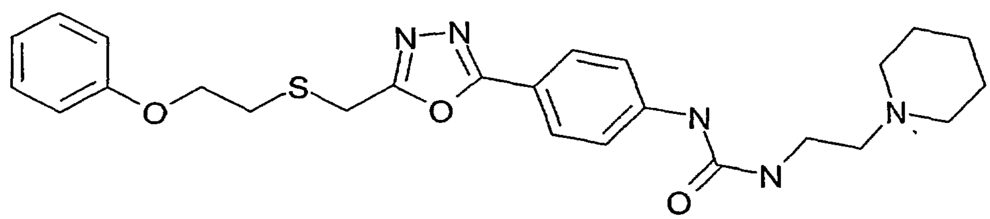


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and 1-(2-aminoethyl)pyrrolidine (0.27 g, 2.4 mmol, 1.2 eq.) to afford 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea as a light brown oil following purification via silica gel flash chromatography using 10% 2M NH3 in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.20 g) in acetone to a warm acetone solution of the amine. After several minutes, a tan solid formed which was collected by filtration leaving 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea oxalate as an off-white solid.

^{1}H NMR (DMSO-d6) δ 9.63 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.65 (d, 2H, J=9 Hz), 7.27 (m, 2H), 7.15 (m, 1H), 6.93 (m, 3H), 4.20 (m, 4H), 3.42 (m, 2H), 3.23 (m, 6H), 3.01 (t, 2H, J=7 Hz), 1.92 (m, 4H). IR ($CHCl_3$, cm^{-1}) 3345, 3230, 1689, 1599, 1541, 1498, 1243, 1224. MS (ES^+) m/e 468. MS (ES^-) m/e 466. Anal. Calcd for $C_{26}H_{31}N_5O_7S$ C, 56.00; H, 5.60; N, 12.56. Found C, 55.52; H, 5.65; N, 12.09. Analytical HPLC 100% purity. MP 111-115°C.

Example 107

Preparation of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea



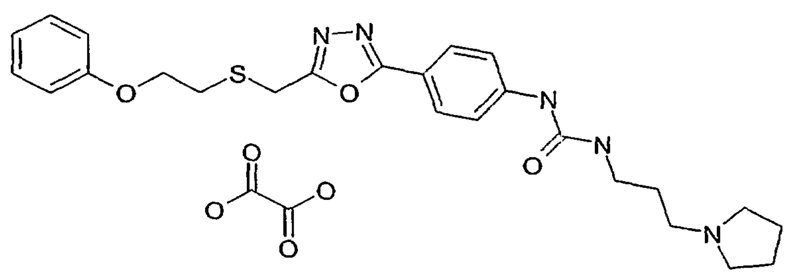
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.70 g, 1.75 mmol, 1 eq.) and 1-(2-aminoethyl)piperidine (0.27 g, 2.1 mmol, 1.2 eq.) to afford 0.79 g (94%) of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea as a yellow oil following purification via silica gel flash chromatography using 10%

2M NH3 in methanol in diethyl ether as the mobile phase. The oil was triturated with diethyl ether/ethyl acetate and the resulting solid collected by filtration leaving 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea (0.50 g) as a yellow solid.

^{1}H NMR (DMSO-d6) δ 9.09 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.59 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.20 (br m, 1H), 4.20 (m, 4H), 3.20 (m, 2H), 3.01 (t, 2H, J=7 Hz), 2.35 (m, 6H), 1.51 (m, 4H), 1.38 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3418, 3358, 3008, 2942, 1690, 1602, 1499, 1244, 1180. MS (ES^+) m/e 482. MS (ES^-) m/e 480. Anal. Calcd for $C_{25}H_{31}N_5O_3S$ C, 62.35; H, 6.49; N, 14.54. Found C, 62.07; H, 6.39; N, 14.33. Analytical HPLC 100% purity. MP 126-128°C.

Example 108

Preparation of 1-{4-[5-(4-Phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate

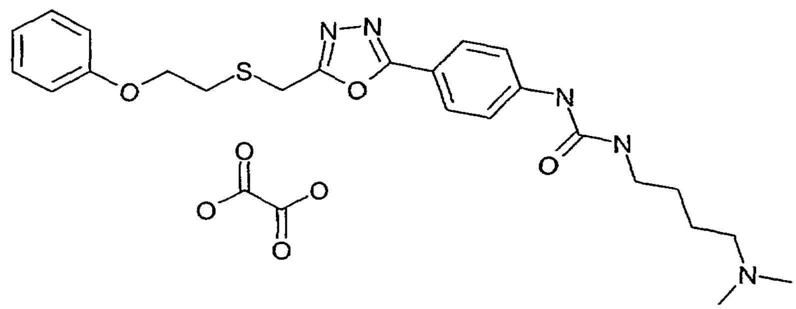


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and 1-(3-aminopropyl)pyrrolidine (0.31 g, 2.4 mmol, 1.2 eq.) to afford 0.64 g (67%) of 1-{4-[5-(4-phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea as a tan foam following purification via silica gel flash chromatography using 10% 2M NH3 in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.13 g) in acetone to an acetone solution of the free base. The resultant solid was collected by filtration and crystallized from methanol to afford 0.39 g of 1-{4-[5-(4-phenoxy-butyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate as an off-white solid.

^{1}H NMR (DMSO-d6) δ 9.44 (s, 1H), 7.82 (d, 2H, J=9 Hz), 7.63 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 4H), 4.20 (m, 4H), 3.17 (m, 8H), 3.01 (t, 2H, J=7 Hz), 1.92 (m, 4H), 1.81 (m, 2H). IR (KBr, cm^{-1}) 3364, 3293, 3041, 2932, 2877, 1691, 1600, 1541, 1497, 1417, 1316, 1236, 1179, 843, 757. MS (ES$^+$) m/e 482. MS (ES$^-$) m/e 480. Anal. Calcd for $C_{27}H_{33}N_5O_7S$ C, 56.73; H, 5.82; N, 12.25. Found C, 56.24; H, 6.08; N, 12.11. Analytical HPLC 97.8% purity. MP softening at 122°C then 126-128°C.

Example 109

Preparation of 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



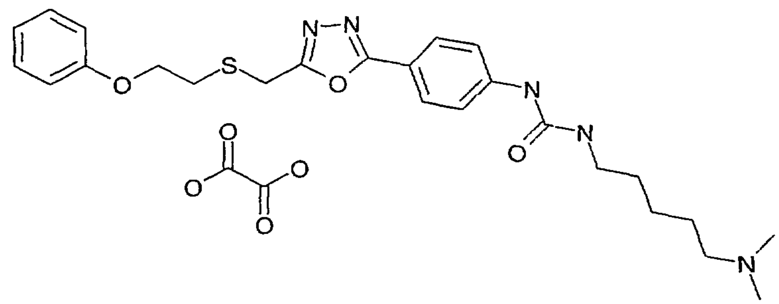
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.87 g, 2.18 mmol, 1 eq.) with 4-dimethylaminobutylamine (0.30g, 2.62 mmol, 1.2 eq.) to afford 1.0 g (98%) of 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification via silica gel flash chromatography using 10% 2M NH3 in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.1 eq of oxalic acid in acetone to an acetone solution of the free base. The 1-(4-dimethylamino-butyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate (0.74 g) was collected by filtration leaving a yellow solid.

^{1}H NMR (DMSO-d6) δ 9.54 (s, 1H), 7.81 (d, 2H, J=9 Hz), 7.64 (d, 2H, J=9 Hz), 7.27 (m, 2H), 7.11 (br t, 1H), 6.93 (m, 3H), 4.20 (m, 4H), 3.13 (m, 2H), 3.02 (m, 4H), 2.74 (s, 6H), 1.65 (m, 2H), 1.47 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3311, 3010, 1778, 1693, 1656, 1601, 1499, 1417, 1318, 1241, 1224, 1180. MS (ES$^+$) m/e 470. MS(ES$^-$) m/e 468.

Anal. Calcd for $C_{26}H_{33}N_5O_7S$ C, 55.80; H, 5.94; N, 12.51. Found C, 54.87; H, 5.63; N, 12.30. Analytical HPLC 100% purity. MP softening at 60°C then 75-78°C.

EXAMPLE 110

Preparation of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate

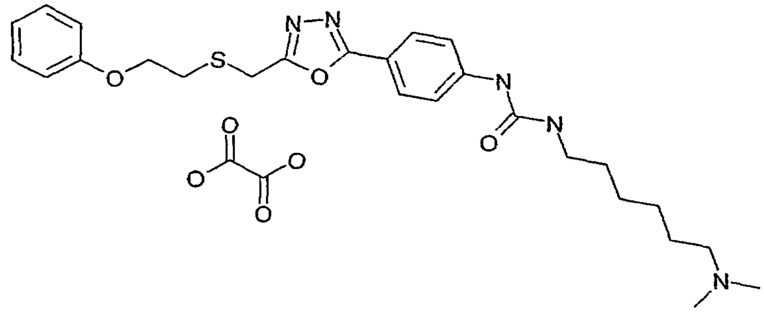


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) with 5-(dimethylamino)pentylamine (0.31 g, 2.4 mmol, 1.2 eq.) to afford 0.92 g (95%) of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a dark yellow oil following purification via silica gel flash chromatography using 7.5% 2M NH3 in methanol in diethyl ether as the mobile phase. The oil was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.19 g) in acetone to an acetone solution of the free base. The solid that formed was collected by filtration to afford 0.73 g of 1-(5-dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-white solid.

^{1}H NMR (DMSO-d6) δ 9.33 (s, 1H), 7.81 (d, 2H, J=9 Hz), 7.62 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.79 (br t, 1H), 4.19 (m, 4H), 3.10 (m, 2H), 3.01 (m, 4H), 2.73 (s, 6H), 1.63 (m, 2H), 1.47 (m, 2H), 1.31 (m, 2H). IR (KBr, cm^{-1}) 3394, 2937, 1696, 1600, 1541, 1499, 1416, 1405, 1318, 1233, 1179, 1083, 1032, 721. MS (ES$^+$) m/e 484. MS (ES$^-$) m/e 482. Anal. Calcd for $C_{27}H_{35}N_5O_7S$ C, 56.53; H, 6.15; N, 12.21. Found C, 56.47; H, 6.21; N, 11.98. MP softening at 77°C then 82-85°C.

Example 111

Preparation of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate

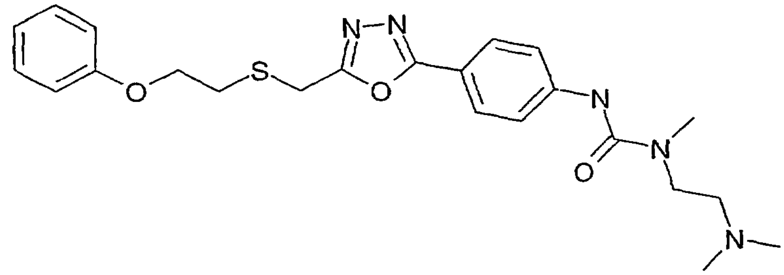


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) with 6-(dimethylamino)hexylamine (0.35 g, 2.4 mmol, 1.2 eq.) to afford 0.97 g (98%) of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a dark yellow oil following purification via silica gel flash chromatography using 7.5% 2M NH3 in methanol in diethyl ether as the mobile phase. The oil was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.21 g) in acetone to an acetone solution of the free base. The solid that formed was collected by filtration to afford 0.94 g of 1-(6-dimethylamino-hexyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-white solid. The solid was recrystallized from methanol/acetone to give an off-white crystalline solid.

^{1}H NMR (DMSO-d6) δ 9.32 (s, 1H), 7.80 (d, 2H, J=9 Hz), 7.62 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.78 (br t, 1H), 4.20 (m, 4H), 3.09 (m, 2H), 2.99 (m, 4H), 2.72 (s, 6H), 1.59 (m, 2H), 1.44 (m, 2H), 1.31 (m, 4H). IR (KBr, cm^{-1}) 3334, 3041, 2931, 2859, 1690, 1600, 1543, 1498, 1244, 1179. MS (ES$^+$) m/e 498. MS (ES$^-$) m/e 496. Anal. Calcd for $C_{28}H_{37}N_5O_7S$ C, 57.23; H, 6.35; N, 11.92. Found C, 56.55; H, 6.21; N, 11.69. Analytical HPLC 95% purity. MP softening at 100°C then 105-108°C.

Example 112

Preparation of 1-(2-dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea

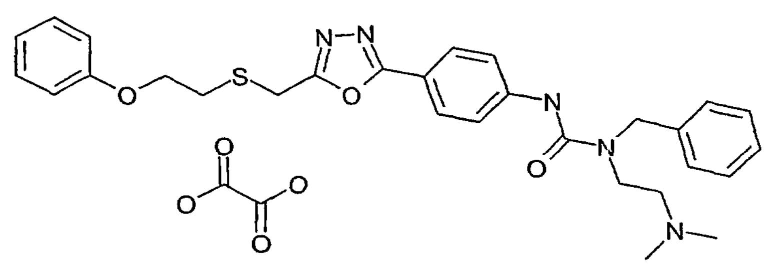


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N,N,N'*-trimethylethylenediamine (0.25 g, 2.4 mmol, 1.2 eq.) to afford 0.73 g (80%) of 1-(2-dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a light yellow solid following purification via silica gel flash chromatography using 10% 2M NH3 in methanol in diethyl ether as the mobile phase.

^{1}H NMR (DMSO-d6) δ 9.63 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.62 (m, 2H), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.40 (t, 2H, J=7 Hz), 3.02 (t, 2H, J=7 Hz), 2.95 (s, 3H), 2.45 (m, 2H), 2.24 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3008, 2953, 2862, 2791, 1674, 1603, 1542, 1499, 1470, 1390, 1317, 1243, 1180. MS (ES^+) m/e 456. MS (ES^-) m/e 454. Anal. Calcd for $C_{23}H_{29}N_5O_3S$ C, 60.64; H, 6.42; N, 15.37. Found C, 60.34; H, 6.29; N, 15.17. Analytical HPLC 99% purity. MP softening at 121°C then 134-135°C.

Example 113

Preparation of 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate



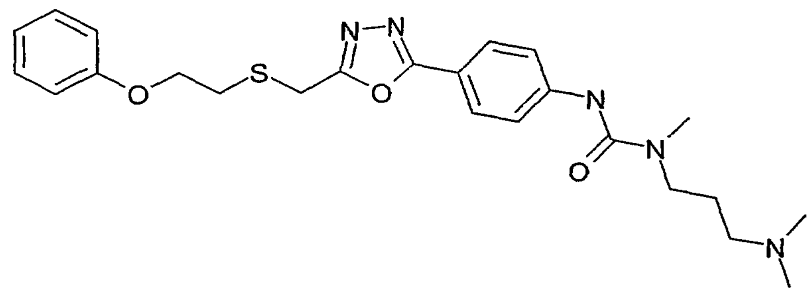
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-

[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N'*-benzyl-*N,N*-dimethylethylenediamine (0.43 g, 2.4 mmol, 1.2 eq.) to afford 0.89 g (84%) 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a yellow oil following purification via silica gel flash chromatography using 5% 2M NH3 in methanol in diethyl ether as the mobile phase. The free base was converted to the oxalate salt by adding 1.2 eq. of oxalic acid (0.18 g) in acetone to an acetone solution of the free base. Addition of diethyl ether to the cloud point and cooling produced 0.98 g of 1-benzyl-1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as an off-white solid.

^{1}H NMR (DMSO-d6) δ 9.43 (s, 1H), 7.86 (d, 2H J=9 Hz), 7.73 (d, 2H, J=9 Hz), 7.38 (m, 2H), 7.28 (m, 5H), 6.93 (m, 3H), 4.69 (m, 2H), 4.19 (m, 4H), 3.58 (m, 2H), 3.09 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.69 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3306, 3009, 1777, 1661, 1601, 1499, 1316, 1242, 1224. MS (ES^+) m/e 532. MS(ES^-) m/e 530. Anal. Calcd for $C_{31}H_{35}N_5O_7S$ C, 59.89; H, 5.67; N, 11.26. Found C, 58.66; H, 5.32; N, 11.23. Analytical HPLC 98% purity. MP softening at 70°C then 72-76°C.

Example 114

Preparation of 1-(3-dimethylamino-propyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea



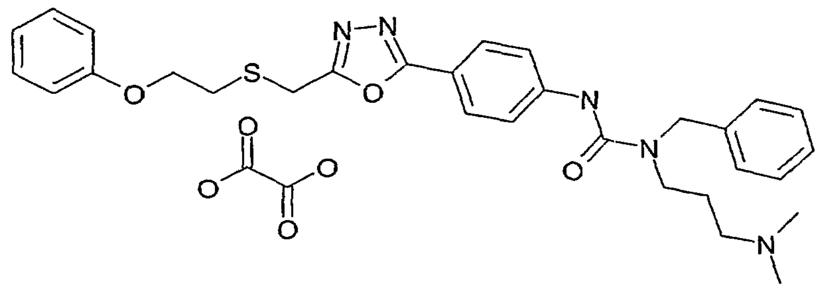
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e, from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N,N,N'*-trimethyl-1,3-propanediamine (0.24 g, 2.1 mmol, 1.2 eq.). to afford 0.51 g (62%) of 1-(3-dimethylamino-propyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as a crystalline orange solid following purification by

silica gel flash chromatography using 10% 2M NH3 in methanol in chloroform as the mobile phase and recrystallization from EtOAc/Et2O.

^{1}H NMR (DMSO-d6) δ 9.66 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.62 (m, 2H), 7.27 (M, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.32 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.89 (s, 3H), 2.29 (m, 2H), 2.23 (s, 6H), 1.70 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3008, 2950, 2827, 2787, 1665, 1604, 1498, 1229, 1179. MS (ES^+) m/e 470. MS (ES^-) m/e 468. Anal. Calcd for $C_{24}H_{31}N_5O_3S$ C, 61.38; H, 6.65; N, 14.91. Found C, 60.75; H, 6.49; N, 14.43. Analytical HPLC 99% yield. MP softening at 114°C then transition at 116-118°C then melting at 136-139°C.

Example 115

Preparation of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate

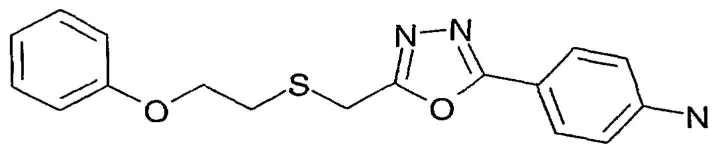


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-carbamic acid ethyl ester (0.80 g, 2.0 mmol, 1 eq.) and *N'*-Benzyl-*N,N*-dimethyl-propane-1,3-diamine (0.46 g, 2.4 mmol, 1.2 eq.) to afford 0.80 g (73%) of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea as an orange oil following purification by silica gel flash chromatography using 5% 2M NH3 in methanol in chloroform as the mobile phase. The free base was converted to the oxalate salt by adding 1.2 eq. of oxalic acid (0.14 g) in acetone to an acetone solution of the free base. Addition of diethyl ether to the resulting yellow solution and cooling produced 0.62 g of 1-benzyl-1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea oxalate as a tan solid.

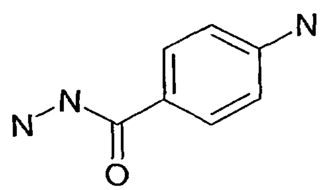
[1]H NMR (DMSO-d6) δ 9.03 (s, 1H), 7.85 (d, 2H, J=9 Hz), 7.75 (d, 2H, J=9 Hz), 7.37 (m, 2H), 7.27 (m, 5H), 6.93 (m, 3H), 4.66 (m, 2H), 4.19 (m, 4H), 3.37 (m, 2H), 3.00 (m, 4H), 2.69 (s, 6H), 1.88 (m, 2H). IR (KBr, cm^{-1}) 3435, 1723, 1653, 1599, 1524, 1498, 1234, 838, 703. MS (ES^+) 546. MS (ES^-) m/e 544. Anal. Calcd for $C_{32}H_{37}N_5O_7S$ C, 60.46; H, 5.87; N, 11.02. Found C, 60.14; H, 5.60; N, 10.60. Analytical HPLC 99% purity. MP softening at 117°C then 159-164°C.

Example 116

Preparation of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine



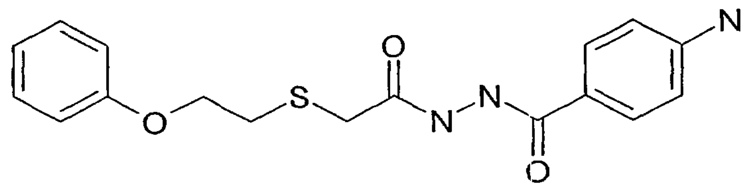
a) 4-Amino-benzoic acid hydrazide



A solution of methyl 4-aminobenzoate (10 g, 66.15 mmol, 1 eq.) and hydrazine hydrate (40 mL) in absolute ethanol (120 mL) was allowed to reflux for 16 h. The solvent was removed in vacuo and the resulting off-white solid was triturated with hot ethyl acetate. The solid was collected by filtration to afford 9.1 g (91%) of 4-amino-benzoic acid hydrazide as an off-white solid.

1H NMR (DMSO-d6) δ 9.25 (s, 1H), 7.53 (d, 2H, J=9 Hz), 6.52 (d, 2H, J=9 Hz), 5.56 (s, 2H), 4.32 (s, 2H). IR (KBr, cm-1) 3428, 3348, 3308, 3233, 1630, 1604, 1504, 1321, 1306, 958, 842. MS (ES+) m/e 152. MS (ES-) m/e 150. Anal. Calcd for $C_7H_9N_3O$ C, 55.62; H, 6.00; N, 27.80. Found C, 55.93; H, 6.21; N, 27.53.

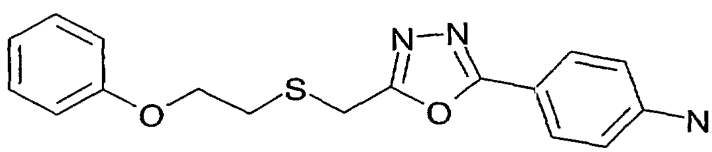
b) 4-Amino-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101c, from (2-phenoxyethylthio)acetic acid (4.25 g, 20.0 mmol, 1 eq.) and 4-amino-benzoic acid hydrazide (3.33 g, 22.0 mmol, 1.1 eq.) to afford 5.85 g (85%) of 4-amino-benzoic acid *N'*-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide as a yellow foam following purification by silica gel flash chromatography using a step gradient of acetone in hexane as the mobile phase.

^{1}H NMR (DMSO-d6) δ 9.91 (s, 2H), 7.60 (d, 2H, J=9 Hz), 7.28 (m, 2H), 6.95 (m, 3H), 6.55 (d, 2H, J=9 Hz), 4.19 (t, 2H, J=7 Hz), 3.31 (s, 2H), 3.03 (t, 2H, J=9 Hz). IR (KBr, cm^{-1}) 3450, 3357, 3268, 3214, 1696, 1627, 1611, 1592, 1562, 1482, 1291, 1242, 1173, 837. MS (ES$^+$) m/e 346. MS (ES$^-$) m/e 344. Anal. Calcd for $C_{17}H_{19}N_3O_3S$ C, 59.11; H, 5.54; N, 12.16. Found C, 59.13; H, 5.79; N, 12.09.

c) 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine

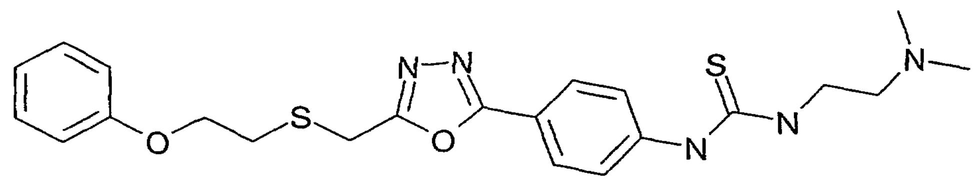


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101d, from 4-amino-benzoic acid *N'*-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (11.42 g, 33.06 mmol) to afford 10.77 g (99%) of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine as a yellow solid following purification by silica gel flash chromatography using a step gradient of ethyl acetate in hexane as the mobile phase.

^{1}H NMR (DMSO-d6) δ 7.60 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 6.66 (d, 2H, J=9 Hz), 5.93 (m, 2H), 4.18 (m, 4H), 3.00 (t, 2H, J=7 Hz). IR ($CHCl_3$, cm^{-1}) 3011, 1624, 1610, 1501, 1243, 1180. MS (ES+) m/e 328. Anal. Calcd for $C_{17}H_{17}N_3O_2S$ C, 62.37; H, 5.23; N, 12.83. Found C, 61.61; H, 5.12; N, 12.50. Analytical HPLC 97.8% purity. MP 126-130°C.

Example 117

Preparation of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea

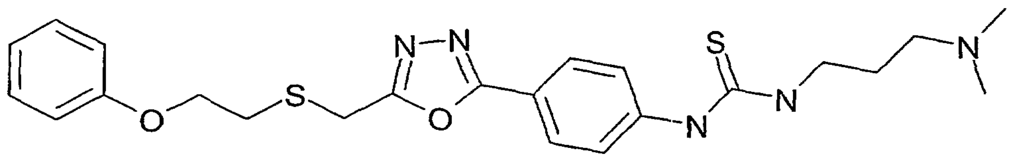


A solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (5.21 g, 15.92 mmol, 1 eq., prepared in Example 119) in anhydrous acetonitrile was treated with 1,1'-thiocarbonyldiimidazole (3.15 g, 15.92 mmol, 1 eq.) as a solid and stirred at room temperature for 16 h. The solvent was removed *in vacuo* leaving imidazole-1-carbothioic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a brown oil. A portion of one-half of this material (7.96 mmol) was dissolved in anhydrous DMF and treated with *N,N*-dimethylethylenediamine (0.84 g, 9.55 mmol, 1.2 eq.). The resulting mixture was heated at 100°C for 1.5 h, cooled, then diluted with EtOAc and washed with 50% brine. The organic layer was collected, dried over MgSO4, filtered, and the solvent removed *in vacuo* leaving a yellow oil. The residue was purified by preparative HPLC to afford 2.33 g (64%) of 1-(2-dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea as a yellow oil which later crystallized. A portion of material was recrystallized from ethyl acetate to afford an off-white solid.

^{1}H NMR (DMSO-d6) δ 10.06 (s, 1H), 7.84 (m, 5H), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.56 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.45 (m, 2H), 2.20 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3429, 3407, 3007, 2982, 2956, 2829, 2781, 1731, 1614, 1601, 1497, 1337, 1243, 1173. MS (ES^+) m/e 458. MS (ES^-) m/e 456 Anal. Calcd for $C_{22}H_{27}N_5O_2S_2$ C, 57.74; H, 5.95; N, 15.30. Found C, 57.60; H, 5.88; N, 14.89. Analytical HPLC 96.9% purity. MP 155-158°C.

Example 118

Preparation of 1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea

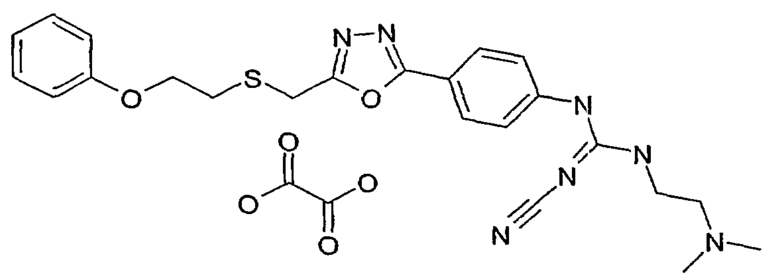


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 117, from {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide (7.96 mmol, 1 eq) and 3-dimethylaminopropylamine (0.98 g, 9.55 mmol, 1.2 eq.) to afford 2.87 g (77%) of 1-(3-dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-thiourea as a yellow oil which started to crystallize following purifiication by preparative HPLC. A small portion was recrystallized from ethyl acetate giving an off-white solid.

^{1}H NMR (DMSO-d6) δ 9.86 (s, 1H), 8.25 (s, 1H), 7.89 (d, 2H, J=9 Hz), 7.70 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.50 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.21 (t, 2H, J=7 Hz), 2.10 (s, 6H), 1.68 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3411, 2980, 2952, 2862, 2827, 2787, 1615, 1601, 1588, 1532, 1499, 1469, 1307, 1242. MS (ES^+) m/e 472. MS (ES^-) m/e 470. Anal. Calcd for $C_{23}H_{29}N_5O_2S_2$ C, 58.57; H, 6.20; N, 14.85. Found C, 59.11; H, 6.49; N, 14.85. Analytical HPLC 97.9% purity. MP 136-139°C.

Example 119

Preparation of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate



Diphenyl cyanocarbonimidate (1.53 g, 6.42 mmol, 1.05 eq.) was added to a yellow solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (2.0 g, 6.11 mmol, 1 eq., prepared in Example 116) in 50 mL of anhydrous acetonitrile. The resultant solution heated at reflux for 16 h. The solvent was removed in vacuo to